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(54) Infection-resistant compositions, medical devices and surfaces and methods for preparing and using same.

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WO-A-86/02006
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JOURNAL OF APPLIED BACTERIOLOGY, vol.
45, 1978, pages 397-405, The Society for Ap-
plied Bacteriology; L.B. QUESNEL et al.:
"Synergism between chlorhexidine and sul-
phadiazine"

(73) Proprietor : THE TRUSTEES OF COLUMBIA
UNIVERSITY IN THE CITY OF NEW YORK
630 West 168th Street
New York, NY 10032 (US)

(72) Inventor : Fox, Charles L., Jr.
290 West End Avenue Apartment 4C
New York, NY 10023 (US)
Inventor : Modak, Shanta M.
184 Howland Avenue River Edge
New Jersey, NJ 07661 (US)
Inventor : Sampath, Lester A.
7 Lawrence Street Nyack
New York, NY 10960 (US)

(74) Representative : Lucas, Brian Ronald et al
Lucas, George & Co. 135 Westhall Road
Warringham Surrey CR3 9HJ (GB)

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Description

This invention relates to infection-resistant compositions, medical devices and surfaces and to methods for using and preparing the same.

Medical devices for use externally or internally with humans or animals can serve to introduce bacterial, viral, fungal or other undesirable infections. Certain prior art devices become unworkable after a short period of time, and must be replaced. In the case of urinary catheters, for example, frequent replacement can cause excessive discomfort to the patient and prolonged hospitalization. In the case of intravenous catheters used for critical care patients, infections can themselves prove life threatening. Additionally, there is always a threat of exposure to infectious contamination from surfaces that contact patients, from surgical gloves, and from other medical gear and apparatus.

To prevent such contamination, medical devices can be treated with an antimicrobial agent. Known methods of preparing an infection-resistant medical device have been proposed in US Patents Nos. 3,556,874, 3,674,901, 3,695,921, 3,705,938, 3,987,797, 4,024,871, 4,318,947, 4,381,380, 4,539,234 and 4,612,337.

In addition, antimicrobial compositions useful as coatings for medical devices or for forming the device itself are disclosed in US Patents Nos. 3,699,956, 4,054,139, 4,592,920, 4,603,152 and 4,667,143.

However, such known methods are somewhat complicated or deficient in the results obtained. The art has great need for medical devices which are able to resist microbial infection when placed in the area of the body to which it is applied and which provide this resistance over the period of time which it remains in place. At the same time, these desirable characteristics must be achieved without sacrifice of other well recognized desirable characteristics. In the case of catheters, for example, it is important that any coating thereon leave a surface which provides a minimum of resistance to insertion of the catheter and which does not release a toxic substance to be absorbed by the body.

Furthermore, some uses of antimicrobial metal compounds including silver salts in antimicrobial coatings for medical devices are known, for example from EP-A-190 504. Also, chlorhexidine and its salts are known to be powerful antiseptics, but the combination of chlorhexidine with silver nitrate has been shown to have prophylactic properties in burn therapy. In addition, the combination of chlorhexidine and sulfadiazine is known in topical applications to exhibit synergism against strains of *Pseudomonas*, *Proteus*, and *Staphylococcus*, as disclosed in Quesnel et al, *Synergism between Chlorhexidine and Sulphadiazine*, Journal of Applied Bacteriology, 1978, 45, 397-405.

Summary of the Invention

A principal object of the present invention, is to provide an improved method of preparing an infection-resistant medical device which will impart antimicrobial activity to the medical device through a sustained and controlled activity rate over an appreciable period of time, without hampering the biocompatibility of the surface and other intended functions of the device. A further object of the present invention is to provide an infection-resistant medical device having superior antimicrobial properties.

Still another object of the present invention is to provide an antimicrobial composition useful in providing an antimicrobial coating on medical devices.

In accordance with a first aspect of the present invention, there is provided a method of preparing an infection-resistant surface, characterized by

- (a) preparing a coating vehicle by dispersing a matrix-forming polymeric material selected from the group consisting of biomedical polyurethane, biomedical silicones, biodegradable polymers and combinations thereof in at least one solvent therefor;
- (b) incorporating an antimicrobial agent comprising a silver salt and a biguanide in the coating vehicle to form a coating composition;
- (c) coating the surface with the coating composition; and
- (d) drying the coating.

According to another aspect of the invention there is provided a method of preparing an infection-resistant surface, characterized by preparing a first coating vehicle by dispersing a biomedical polyurethane in a solvent therefor, and optionally from 0.2 to 2% polylactic acid, and incorporating therein an antimicrobial agent comprising a silver salt and a biguanide; preparing a second coating vehicle by dispersing a biomedical silicone in a solvent therefor preferably at a concentration of 0.5 to 5%; applying said first coating vehicle to the surface and allowing it to form an adherent first coating; and applying said second coating over said first coating to form a second coating adherent to said first coating.

In accordance with a further aspect of the present invention, there is provided a coating vehicle comprising a biomedical polyurethane in at least one solvent therefor and an antimicrobial agent comprising a silver salt

and a biguanide.

In accordance with a further aspect of the present invention there is provided a method of preparing an infection-resistant medical device which comprises preparing a mixture of silver or a silver salt such as silver sulfadiazine or silver carbonate and a biguanide, and applying said mixture to the surface of a medical device.

A further aspect of the invention provides a method of preparing an infection-resistant medical device which comprises preparing a mixture of (i) a substance selected from the group consisting of chlorhexidine and its salts and (ii) a silver salt selected from the group consisting of silver sulfadiazine, silver acetate, silver benzoate, silver iodate, silver laurate, silver protein, silver chloride, silver palmitate, silver oxide, silver carbonate and silver nitrate, and applying the mixture to the surface of a medical device.

There is also provided a method of preparing an infection-resistant medical device which comprises preparing a mixture of chlorhexidine acetate and silver sulfadiazine in proportions by weight ranging from 1:9 and 9:1, applying the mixture to the surface of a medical device.

Other aspects of the invention provide a method of impregnating expanded PTFE medical devices, particularly vascular grafts, which comprises preparing a coating vehicle comprising biomedical polyurethane (for example in an amount of 0.25-1%) and a biodegradable polymer, preferably polylactic acid (e.g., in an amount of 0.25-1%), in a solvent therefor (e.g., 25% NEP and 75% THF) together with at least one member of a group consisting of chlorhexidine and its salts (e.g., 1% of chlorhexidine acetate) and piperacil (e.g., 3%) as antimicrobial agents, placing said graft in contact with the coating vehicle while under reduced atmospheric pressure, and drying the treated graft; and an expanded PTFE vascular graft, a substantial portion of the interstices of which contains a coating composition comprising, by weight, one part biomedical polyurethane, one part polylactic acid, one part chlorhexidine acetate and three parts piperacil.

The invention further provides a method of imparting infection-resistance to medical devices comprised of expanded PTFE materials comprising the step of applying to the device a coating vehicle comprising a biodegradable polymer, a silver salt and a biguanide. The device may be first dipped into a suspension of silver sulfadiazine, chlorhexidine acetate and biodegradable polymer in alcohol-tetrafurane (10:90), followed by dipping the device into alcoholic silver nitrate solution.

Detailed Description of the Invention

Surfaces which may embody the present invention can be generally any surfaces that contact patients or are important in health care, including table tops, hospital beds and various specific medical devices.

Medical devices are those for use both externally and internally and include, for example, urinary, both internal and external, and intravenous catheters, contraceptives such as condoms, medical gloves, such as surgical and examination gloves, wound dressings, drainage tubes, orthopedic, penile and other implants, wound clips, sutures, hernia patches and arterial grafts. The devices or surfaces, sometimes generally together referred to as "surfaces" herein, can be made of a variety of natural or synthetic materials such as metals, plastics and polymers, and including Dacron®, rubber, latex, collagenous substances, silicone, polyurethane, polyvinyl chloride, Teflon®, polypropylene, polyethylene, poly(lactic acid), polyglycolic acid, cotton, silk, stainless steel, porous ceramics, and porcelain.

Definitions

The following specification refers to a number of microorganisms in describing the invention or its use. Unless otherwise stated, the following are the generally recognized names of the microorganisms, together with their source:

<u>Organism</u>	<u>Source</u>
<u>Staphylococcus aureus</u>	clinical isolate- Columbia Presbyterian Hospital New York, New York
<u>Staphylococcus epidermidis</u>	clinical isolate- Columbia Presbyterian Hospital New York, New York
<u>Escherichia coli</u>	clinical isolate- Columbia Presbyterian Hospital New York, New York
<u>Candida albicans</u>	ATCC No. 11651

It is also noted that unless otherwise stated, the concentrations and ranges expressed as percentages (%), indicates the respective value based on weight of solid per volume of solvent. As an example, a 1% polyurethane in a solvent coating vehicle comprising tetrahydrofuran (THF) represents 1 gram of polyurethane in 100 ml of THF. On the other hand, in expressing relative proportions of two or more solvents in a coating vehicle, the percentages given are on a vol/vol basis.

Polymeric Coating Agent

The polymeric coating agent component of the coating vehicle of the present invention is selected from the group consisting of biomedical polyurethanes, biomedical silicones, biodegradable polymers and combinations thereof. It has been found that these particular polymeric materials enable the antimicrobial agent of the second embodiment of the invention to be retained and released in an active state on the coated medical device over an appreciable period of time, e.g., from about 12 to in excess of 21 days.

Selection of the coating vehicle depends upon the specific composition of the surface of the device to be coated, and the characteristics sought. For example, a polyurethane catheter is preferably coated with a formulation based on a biomedical polyurethane matrix-forming material. A silicone rubber catheter, on the other hand, preferably is provided with a coating having a silicone rubber as a matrix-forming material. It has also been discovered that a final thin coat of a silicone fluid after a first coating of biomedical polyurethane or of silicone rubber imparts surface glossiness and lubricity to the catheter. Thus, multiple, combined coatings, described in greater detail below, can also be achieved with improved characteristics.

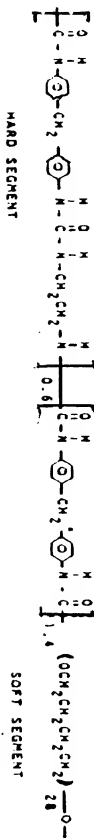
In addition to polymeric coating compositions, the antimicrobial compositions of this invention may be applied to surfaces of medical devices in powder form, preferably under conditions which cause adherence of the powder to the surface of the device. For example, medical gloves, such as surgical or examination gloves fabricated from latex, polyurethane or polyvinyl acetate, may be coated with a powder containing the antimicrobial composition, as will be explained below in more detail.

A. Biomedical Polyurethane

In accordance with the first embodiment of the invention, the essential polymeric coating agent component of the coating vehicle is biomedical polyurethane, since it has been found unexpectedly that polymeric materials of this class enable the antimicrobial agent to be retained in an active state on the coated medical device and released over an appreciable period of time, e.g., from about 12 to in excess of 21 days, without altering the biocompatibility, lubricity and non-thrombogenicity of the surface. Suitable biomedical polyurethanes include both the ether-based polyurethanes and the ester-based polyurethanes described on pages 175-177 of Controlled Release of Biologically Active Agents, by Richard W. Baker, John Wiley and Sons, 1987; the ether-based compounds are preferred. A thorough discussion of a number of proprietary biomedical polyurethanes is found in Polyurethanes in Medicine, by Michael D. Lelah and Stuart L. Cooper, CRC Press, Inc., Fla 1986, pp. 57-67.

The following is a listing of proprietary biomedical polyurethanes that are useful in accordance with the invention:

1. Biomer®, which consists of 4,4-diphenylmethane-diisocyanate (MDI) and low molecular weight polytetramethyleneoxide (PTMO) segments with diamines as chain extenders. A proposed repeat unit chemical structure for Solution Grade Biomer® is:



2. Acuthane® is a block copolymer which contains 10% polymethylsiloxane and 90% polyetherurethane.

3. Pellethane® is an aromatic ether polyurethane. Pellethane® 2363 (80AE) is not crosslinked and is readily soluble in dimethylacetamide, tetrahydrofuran, or N-ethyl pyrrolidone. The 90A of the same series contains crosslinks due to the excess of isocyanates present during the polymerization process and is therefore more difficult to solubilize.

4. Rimplast® is a silicone urethane made with either aliphatic or aromatic ethers or esters of polyurethane and a reactive, high molecular weight silicone to form an interpenetrating network (IPN).

We have found that best results are obtained using Pellethane® 2363-80AE, one of a series of thermoplastic, segmented elastomers sold under the designation Pellethane® by Dow Chemical Co. These materials are described at p. 60 of Lelah et al, supra. Another suitable product is Biomer®, which is conveniently available as a 30 wt.% solution in N, N-dimethylacetamide (DMAC) described at pp. 57-58 of Lelah et al, supra. Another suitable material is Rimplast®, a series of biomedical urethanes containing silicones, reacted to form a series of interpenetrating network modified silicones containing polyurethanes. A description of these materials are found on pp. 61-63 of Lelah et al, supra.

The prior art, such as U.S. 4,667,143, fails to distinguish between various polymeric coating agents. The patent states that any one of a long list of resins may be mixed with an antimicrobial metal compound to provide antimicrobial coatings on medical devices. The working examples of the patent utilize either ABS polymers or alkoxy curing RTV silicone rubbers. Quite unexpectedly we have found that the specific application of biomedical polyurethanes as a coating agent is superior to all other known polymeric coating materials. This discovery was made by first determining the relative solubilities of various polymeric coating agents in equal amounts of DMAC and ethylacetate. The results of this screening test are shown in Table I.

TABLE I

Solubility of Various Polymers in Solvent Comprising
50% DMAC + 50% Ethyl Acetate

1.	POLY (ETHYLENE)	NS
2.	POLY (METHYL METHACRYLATE)	S
3.	POLY (ETHYLENE-MALEIC ANHYDRIDE)	NS
4.	POLY (CAPROLACTONE)	S
5.	POLY (VINYL ALCOHOL) MW 25,000	NS
6.	POLY-3-HYDROXYBUTYRATE 5x10 ⁵	NS
7.	POLY (ETHYLENE OXIDE) MW 4,000,000	NS
8.	POLY (BUTANEDIOL-1, 4-TERE-PHTHALATE)	NS
9.	POLY (HEXAMETHYLENE DODECANEDIAMIDE) NYLON	NS
10.	POLY (VINYL ACETATE) MW 500,000	S
11.	POLY (VILIDENE CHLORIDE-ACRYLONITRILE) 80:20	S
12.	POLY (HEXAMETHYLENE SEBACAMIDE) NYLON	NS
13.	POLY (PROPYLENE, ISOTACTIC)	NS
14.	POLY (ETHYL METHACRYLATE)	S
15.	POLY (STYRENE-MALEIC ANHYDRIDE)	S
16.	POLY (STYRENE ALLYL ALCOHOL)	S
17.	POLYACRYLAMIDE	NS
18.	POLY (ISO-BUTYL METHACRYLATE)	S
19.	POLY (VINYL PYRROLIDONE)	S
20.	POLY (PROPYLENE, CHLORINATED, 65%)	S
21.	POLY (N-BUTYL METHACRYLATE-ISO-BUTYL METHACRYLATE 50/50)	S
22.	POLY (VINYL CHLORIDE-VINYL ACETATE)	S
23.	POLY (ACRYLIC ACID) MW 4,000,000	NS
24.	POLY (HEXAMETHYLENE ADIPAMIDE)	NS
25.	POLY (N-BUTYL METHACRYLATE)	S
26.	POLY (CARBONATE BISPHENOL A)	NS
27.	POLY (LAURYL LACTIM)	NS
28.	POLY (CAPROLACTAM)	NS
29.	POLY (ACRYLAMIDE-ACRYLIC ACID SODIUM SALT) 70% CARBOXYL HIGH CARBOXYL MW 200,000	NS
30.	POLY (VINYL ALCOHOL) 88% MOLE HYDROLYZED, MW 25,000	NS
31.	POLY (ACETAL) RESIN	NS
32.	POLY (STYRENE-ACRYLONITRILE 75:25)	S
33.	POLY (METHYL VINYL ETHER/MALEIC ANHYDRIDE)	NS
34.	POLY (SULFONE) RESIN	S
35.	POLY (VINYLDIENE FLUORIDE)	S
36.	POLY (TETRAFLUOROETHYLENE)	NS
37.	POLY (VINYLDIENE CHLORIDE/VINYL CHLORIDE 86:12)	S
38.	POLY (VINYL BUTYRAL) MW 100,000-150,000	S
39.	POLY (p-VINYL PHENOL)	S
40.	POLY (ETHYLENE-ACRYLIC ACID 92:8)	NS
41.	POLYURETHANE (DOW PELLETHANE* 2363-80AE)	S

S = READILY SOLUBLE

NS - NOT SOLUBLE

After rejecting the insoluble polymers, steps were taken to coat the soluble polymers, i.e., those identified in Table I as numbers 2, 4, 10, 11, 14, 15, 16, 18, 19, 20, 21, 22, 25, 32, 34, 35, 37, 38, 39, and 41, upon catheters to determine which formed stable, workable coatings. Both urinary and I.V. catheters were used, and for this test, the urinary catheter was fabricated of latex and the I.V. catheter of Pellethane® 2363, 90A, described above.

Polymer Backbone Rotational Flexibility:

It is well established that apart from the molecular weight of a solute, solubility in a polymer depends on the ability of the backbone of that polymer to rotate about one or more axes. Polyurethane's backbone flexibility falls somewhere in between the extreme freedom of rotation found in the silicone rubbers to the inflexibility of polystyrene. Since polyurethane is a segmented block copolymer made of both hard and soft segments it combines the ability of readily releasing bio-active agents from the amorphous phase with the slow release, reservoir-like characteristics of the hard or crystalline domain. Intramatrix diffusion probably occurs as the bio-active drug levels in the soft domains drop, causing a gradient related flow of solute out of the crystalline phase into the more flexible areas which then in turn diffuses out into the environment.

Progressive Formation of Interconnected Diffusion Channels:

As the drug molecules at the surface of the matrix are dissolved, the solute (blood, perspiration, saline, media etc.) is allowed to penetrate into the film, thus forming micro-channels which further facilitate the release process. The pore formation is likely proportional to the flexibility of the backbone of the polymer, whereby the rate of channeling falls as the domain becomes more crystalline.

Polyurethane has, on the average, 75 to 100 times the water absorption of silicone (RTV) and 25 times that of polystyrene. The greater value for polyurethane is probably due to the hydrophilic nature of the soft segment and presumably means that channel formation is enhanced.

Electrical Properties of the Matrix:

The charge that a polymer carries influence the affinity of the antimicrobial agent for the matrix. In some cases, such as when the antimicrobial agents silver (Ag) or chlorhexidine acetate (CHA) are mixed with latex, the binding is so strong that ions of the antimicrobial agent are restricted in their ability to diffuse out of the matrix. Some biomedical polyurethanes carry a positive charge and therefore do not react with, and thus inactivate, cationic antimicrobial agents such as Ag or CHA. Anionic compounds such as piperacillin or sulfadiazine are relatively unreactive and extremely soluble so that they do not bind to polyurethane and are released at a steady and prolonged rate.

Thus, the polymeric coating agent component cannot be polyethylene vinyl acetate, polyvinyl chloride or polyvinyl alcohol, because such polymers give unsatisfactory results. As mentioned above, the polymer of choice is a polyether polyurethane and, more specifically, Pellethane® 2363-80AE. It has been further found that this polymer in solvent must critically range from 1-10%, and preferably 2-6%, and most preferably 3% by volume, for best performance.

B. Biomedical Silicones

Suitable biomedical silicones include the silicone rubbers or elastomers described on pp. 156-162 of Controlled Release of Biologically Active Agents, by Richard W. Baker, John Wiley and Sons, 1987.

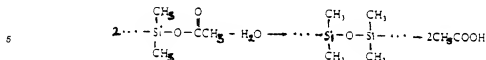
Silicone rubbers having the general formula



where R is either a methyl of a $-C_6H_5$ substituent, are useful. More specifically, the following proprietary biomedical silicones may be used:

1. Silastic® Type A Medical Adhesive, a polydimethyl siloxane sold by Dow Corning and which is a one

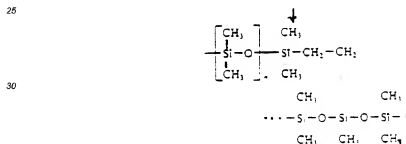
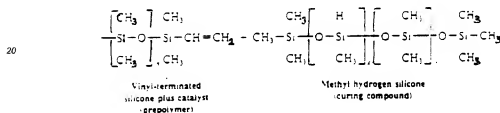
component system which cures at ambient room temperature and humidity. Its formula is:



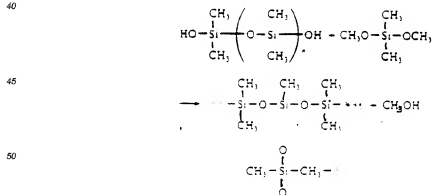
2. Other Silastic® products that can be used to form time release matrices include:

- (a) Q72213 - a medical grade dispersion of silicone in trichloroethane;
- (b) Silastic® 360; and
- (c) MDX4-4159, a proprietary product of Dow Corning containing 50% of an amino functional polydimethyl siloxane copolymer and 50% of mixed aliphatic and isopropanol solvents.

3. Two component vinyl curing silicone - a dimethyl silicone compound with a vinyl terminated prepolymer component is reacted to the backbone of a second silicone component.



4. Two component curing silicone - Silastic® 382 is an example of a silicone which cures by condensation whereby a prepolymer containing a hydroxy group is crosslinked by the addition of a methoxysilane and catalyst.



It is preferred to employ room temperature curing materials. It is also preferred to employ a mixture of equal parts of a polydimethyl siloxane such as Silastic® Type A adhesive and a mixed amino functional polydimethyl siloxane copolymer such MDX4-4159 in mixed aliphatic and isopropanol solvents, to provide a coating surface having a smooth surface and extended period of activity.

The selection of specific polymeric coating agent to form a coating matrix will depend upon the nature of the surface to which the coating will be applied. It is preferred that a biomedical polyurethane be applied to a polyurethane surface to assure good coating adherence. A biomedical silicone, such as a mixture of Silastic® Type A Medical Adhesive and MDX4-4159, is suitable to coat a device that is fabricated of silicone, polyurethane or of latex.

C. Biodegradable Polymers

It has further been found that use of a biodegradable polymer in the coating composition of this invention, either alone or in combination with one or more of the other biomedical polymers, enhances the character of the polymer matrix. Suitable biodegradable polymers include the homopolymers poly(glycolic acid), poly(D-lactic acid), poly(D,L-lactic acid), poly(D,L-ethylglycolic acid), poly(dimethylglycolic acid), poly(D, L-methylthylglycolic acid), and poly(E-caprolactone), as well as biodegradable polyhydroxy butyric acid and mixtures thereof. A preferred biodegradable polymer is polylactic acid (PLA).

Thus biodegradable polymer may be added to biomedical polyurethane in the quantities indicated herein. The biodegradable polymer modulates the rate of release of antimicrobial drugs. The initial burst of drug which occurs during the first few days after implantation is more or less eliminated since the drug is bound in the biodegradable polymer and will be released only when degradation of the polymer occurs. Inclusion of a biodegradable polymer such as PLA in the matrix gives prolonged biocidal activity as confirmed in *in vitro* studies, shown in Table IV, below.

TABLE IV

Enhanced Efficacy of Polyurethane + PLA Matrix

<u>Coating Composition</u>	<u>Days of Activity*</u>
1. 3% DPU + 1% AgSD + 1% CHA	4
2. 3% DPU + 1% PLA + 1% AgSD + 1% CHA	5
DPU = Pellethane® 2363-80AE - Dow Chemical Co.	
PLA = poly (lactic acid) molecular weight of 100000	
AgSD = silver sulfadiazine	
CHA = chlorhexidine diacetate	
Solvent = 25 parts of ethanol and 75 parts of tetrahydrofuran (THF)	

* determined according to the bioassay set forth above with regard to Table III

An additional advantage of using a biodegradable polymer such as PLA in a polyurethane matrix is to allow improved tissue ingrowth simultaneously with a prolonged antimicrobial effect as the biodegradable polymer degrades. Thus, this embodiment of the invention is particularly important in orthopedic applications as well as in such devices as arterial grafts where there is a need for formation of the pseudo-intima or the growth of tissue into the interstices of orthopedic implants and arterial grafts, as well as cuffs which anchor IV catheters in place.

Suitable biomedical poly(lactic) polymers include the poly(L-lactide), poly (D-lactide) and the poly(D,L-lactic acid). These materials are described, *inter alia*, on pp. 87, 88 and 115, of Baker, *supra*, and are biodegradable. Poly(L-lactic) acid is preferred, and those polymers having a range of molecular weights ranging from 2000 to 300,000 have been used with success.

Poly(D, L-lactic acid)



Poly(D-lactic acid)



The poly(lactic acid) polymers are bioerodable, and while they can be used alone, it is preferred that they be combined with either a biomedical polyurethane or a biomedical silicone.

As in the first embodiment of the invention, an additional advantage of using PLA in a polyurethane matrix is to allow improved tissue ingrowth simultaneously with a prolonged antimicrobial effect as the PLA degrades. Thus, this embodiment of the invention is particularly important in orthopedic applications as well as in such devices as hernia patches and arterial grafts where there is a need for formation of the pseudo-intima or the growth of tissue into the interstices of orthopedic implants and arterial grafts, as well as cuffs which anchor I.V. catheters in place.

Solvents

The solvents used in preparing the coating vehicle used in the present invention includes solvents for the biomedical polymeric coating agent and/or the antimicrobial agent, and include acetic acid, methyl acetate, ethyl acetate, hexane, N-N-dimethylacetamide (DMAC), tetrahydrofuran (THF), alcohols (e.g., alkanols), water, N-ethyl-2-pyrrolidone (NEP), n-(2-hydroxy-ethyl)-2-pyrrolidone, n-cyclohexyl-2-pyrrolidone and combinations thereof. The selection of a particular solvent or mixture of solvents will depend upon the specific biomedical polymeric coating agent being used as well as upon the particular antimicrobial agent or combination of agents.

Certain desired solvents for the polymeric coating agent may not be good solvents for an antimicrobial agent of choice. In that case, a solvent is selected which will dissolve the antimicrobial agent and will be miscible with the solvent solution of polymeric coating agent. Thus, a solvent solution of the antimicrobial agent may be combined with the biomedical polyurethane in solution in its solvent and the two solutions thereafter combined to form a uniform mixture.

Another important consideration in selecting a solvent is that the resulting solution will readily adhere to and form a film on the surface to which it is applied. Certain solvent solutions containing certain polymers do not adequately wet latex surfaces, for example, with the result that the coating is discontinuous or non-adherent.

Antimicrobial Agents

Antimicrobial agents used in the invention include the biguanides, especially chlorhexidine and its salts, including chlorhexidine acetate, chlorhexidine gluconate, chlorhexidine hydrochloride, and chlorhexidine sulfate, silver and its salts, including silver acetate, silver benzoate, silver carbonate, silver iodate, silver iodide, silver lactate, silver laurate, silver nitrate, silver oxide, silver palmitate, silver protein, and silver sulfadiazine.

From the above list, unexpectedly, some special combinations have been found. The combination of the biguanides, especially chlorhexidine and its salts with silver salts cause a special synergistic sustaining of antimicrobial action, as described below. Another effective combination is chlorhexidine acetate and piperacil.

Where the antimicrobial agent used is insoluble in the coating vehicle, as is the case with most of the silver salts and the water insoluble chlorhexidine, it is preferred that the agent be very finely subdivided, as by grinding with a mortar and pestle. A preferred product is micronized, e.g., a product wherein all particles are of a size of 5 μ or less. In the case of the preferred silver sulfadiazine, a micronized product may be used.

The antimicrobial agent is preferably employed in the coating vehicle at a level such that the final coating contains from 10 to 70% by weight of the antimicrobial agent. This may be accomplished by providing a concentration of, for example, 0.5 to 3%, preferably 1%, of chlorhexidine acetate and 0.5 to 5%, preferably 1%, of silver sulfadiazine in the coating vehicle.

Unique to the invention is the use of chlorhexidine since such use internally, that is, in the human body, is heretofore unknown. Though there are examples available on the use of chlorhexidine in the bladder, such data is not relevant hereto, since it is not truly an internal use as there is no contact with the patient's circulation.

The absence of even a hint of using chlorhexidine internally is due, at least in part, to its relatively high toxicity and chemical nature (highly polar, reactive, high affinity for lipids and proteinaceous materials), leaving it a poor candidate as a systemic drug. The only way to use chlorhexidine internally is in the time release matrix

system described above that allows for a dose that is non-toxic to the patient but effective against microorganisms.

Coating Vehicle

The coating vehicle is prepared according to the invention by dissolving the polymeric coating agent in a solvent therefor and by combining this solution with a solution or suspension of the antimicrobial agent. These materials can be combined at room temperature or at a slightly elevated temperature with the aid of agitation. It is preferred to employ solvents with readily evaporate from the coating at room temperature, or at an elevated temperature below that which inactivates the antimicrobial agent.

In the case of a preferred antimicrobial composition chlorhexidine acetate, either alone or in combination with silver sulfadiazine, the coating vehicle is prepared by first dissolving the polymeric coating agent such as the biomedical polyurethane in a solvent therefor, such as tetrahydrofuran (THF). The chlorhexidine is then dissolved in a solvent thereof, such as ethanol, water, or preferably N-ethyl-2-pyrrolidone (NEP), which is also miscible with THF.

Other Agents in Coating Matrix

In addition to antimicrobial agents and matrix forming materials, the coatings of the present invention may contain other compatible ingredients to advantage. For example, where anti-blood clotting activity is desired, heparin may be used, preferably at a level of 0.2%. Another useful ingredient is dextran sulfate, preferably also at a level of 0.2%.

In accordance with the method of this invention, the medical device can be coated with the coating composition by known coating techniques, such as dip coating, spray coating, brush coating, roller coating, etc. Moreover, multiple coatings using the same or different polymer matrix-forming agents for each, can be used.

The coated medical device can be dried at room temperature to remove solvent or with the aid of a slightly elevated temperature over an appropriate time period.

The coating method can be repeated to build up a thicker coating on the medical device and/or to use a different antimicrobial agent in each coating, if desired.

In accordance with another preferred embodiment of the invention, the antimicrobial composition of this invention comprising a mixture of a biguanide and a silver salt in powder form is applied directly to the surface of a medical device. The method of application is one which assures adherence of the powder to the surface. One such method applies the powdered antimicrobial agent to an adhesive surface in micro layers so that minimum loss of adhesiveness occurs while imparting a high level of protection against growth of microorganisms to the surface. Other procedures include mixing the powder with adhesive prior to its application, and providing areas on the surface which alternatively contain adhesive and powdered antimicrobial agent. In one preferred method, a powder comprising a mixture of biguanide and a silver salt, most preferably a mixture of silver sulfadiazine and chlorhexidine acetate, was applied to rubber gloves at a point during their manufacture when the rubber was soft and/or semi-molten. The powder was found to adhere well after cooling of the gloves to room temperature.

It will further be understood that the invention does not require coating both the inside and outside of medical devices, especially catheters. In fact, it has been found that some catheters coated only on the outside provide necessary prophylaxis, without chemical or biological interference with the materials added to the body by the catheter. There may be instances when, for example, a coating containing an antimicrobial agent and heparin is applied only on the outside of an I.V. catheter used for providing blood to a patient. In other instances, it is advantageous to apply a coating with the anti-coagulant on the inside of the catheter to prevent clotting blockages. These specific selections are all within the scope of the invention.

Concentrations of the coating vehicle, the antimicrobial composition, the coating composition and resultant coating can be selected as desired and as illustrated by the following representative examples. In the case of the preferred combination of chlorhexidine acetate and silver sulfadiazine, good results have been obtained when the agents are present in a proportion ranging from 1:9 to 9:1, respectively. Further, it is preferred that this combination of antimicrobial agents be present at levels of from 10 to 70% by weight of the final coating.

The invention will be further illustrated by the following examples. Unless indicated otherwise, the silver sulfadiazine (AgSD) used in the examples was a micronized powder product having a particle size of 5 μ or less.

It is recognized, however, that silver or its salts, including silver sulfadiazine, having a larger average particle size are useful according to this invention, and particle size selection will depend on the contemplated use of the medical device.

Example 1

A coating vehicle for use in accordance with the present invention was prepared as follows:

1 gm of chlorhexidine acetate (CHA) was added to 5 cc of N-ethyl-2-pyrrolidone (NEP). The mixture was heated to 50-60°C and agitated in a Vortex® stirrer until the CHA dissolved.

10 cc tetrahydrofuran (THF) was then added to the CHA solution in NEP and the mixture thoroughly agitated to form a uniform solution.

3 gm of Pellethane® 2363-80AE of the Dow Chemical Co. was added to 50 cc of THF. The mixture was warmed to about the boiling point of THF, 65-70°C, and stirring with a Vortex® stirrer was continued until the polyurethane was dissolved.

1 gm of silver sulfadiazine (AgSD) powder was suspended in 35 cc of THF and vigorously agitated in a Vortex® stirrer to form a uniform suspension. The CHA solution in NEP and THF prepared above was then combined with the polyurethane solution and agitated to form a clear solution. As a last step in preparing the coating vehicle, the AgSD suspension in THF was added and the entire mixture agitated to maintain a uniform suspension. Thus was provided a coating vehicle containing 1% CHA and 1% AgSD as antimicrobial agents, together with 3% of the biomedical polyurethane. The solvent in this case was a mixture of solvents comprising 5% NEP and 95% THF. The CHA was in solution in the coating vehicle, while the AgSD was in uniform suspension.

The coating vehicle prepared above was used to coat an I.V. catheter fabricated of Pellethane® 2363-90A. The catheter was dipped in the coating vehicle while the vehicle was being continuously agitated to insure a uniform suspension. The coated catheter was then dried. A tightly adherent coating on the catheter was thus provided. A bioassay of sections of the catheter performed in accordance with the test given above with respect to Table III showed sustained activity against the microorganisms for in excess of eight days.

Example 2

Methods of Preparing I.V. and Urinary Catheters Coated with Soluble Silver Salts and Water Insoluble Chlorhexidine

In certain instances, it is necessary to use antimicrobial agents starting in solution rather than as cominuted solids. Though the invention comprises both, coating with the precursors of certain antimicrobial agents in solution has been found to be best achieved in one of two ways:

Method 1

Coating vehicle contains 1% AgNO_3 + 1-3% water insoluble free-base chlorhexidine + 6% polyurethane in DMAC/ethyl acetate mixture (1:1).

Water insoluble chlorhexidine is first prepared by precipitating the chlorhexidine from chlorhexidine acetate. This chlorhexidine is used for coating purposes in those instances where the chlorhexidine salts are reactive with other ingredients of the coating vehicle. For example, the acetate or gluconate salts of chlorhexidine react with silver nitrate instantly in aqueous solutions with the undesired result that each is inactivated.

Preparation of 100ml coating vehicle. 1gm silver nitrate and 1gm water-insoluble free-base chlorhexidine were dissolved separately in 10ml portions of DMAC. 6gm polyurethane, Pellethane® 2363-80AE, were dissolved in 30ml DMAC and mixed with the silver nitrate and chlorhexidine solutions. 50ml ethyl acetate was mixed with this solution to form a coating vehicle and used for coating.

Method 2

Coating vehicle contains 0.3% AgNO_3 + 0.75% sulfadiazine + 1-2% chlorhexidine + 6% polyurethane in DMAC/ethyl acetate mixture (1:1).

The method of preparation of this coating solution is the same as described in Method 1 except that the sulfadiazine is added to the chlorhexidine solution and a uniform dispersion formed. The medical device (e.g., catheter) is dipped, sprayed or painted, at least once, with this solution.

A series of catheters were coated with the coating solutions prepared by methods 1 and 2 in this example and compared with a commercially available catheter coated with silver oxide. Catheters numbers 2 and 6 were prepared in accordance with method 1 above. Catheters numbers 3, 5 and 7 were prepared by method 2 above. Catheters numbers 1 and 4 were prepared in accordance with the method and using the formulation following Table I, the chlorhexidine in catheter 4 being the water insoluble type referred to in method 1 above.

The tests recorded in Table V are described elsewhere in this specification. The activity in trypticase soy broth (TSB) was determined by the bioassay described as follows:

1. Latex Urinary Catheters: 2 cm sections were soaked in 5 cc of Trypticase Soy Broth (TSB) and challenged with 10^4 CFU of a 1:1 mixture of *Staph. epi* and *E. coli* pre-diluted to 0.3 optical density at 600 nm.
2. Polyurethane LV: 2 cm sections soaked as above and challenged with 10^4 CFU of *Staph. aureus*.

The zone of inhibition determination was made following Bioassay A, described in Example 5. The Agar Lumen test was conducted as follows:

5 cc of trypticase soy agar (TSA) was solidified in a culture tube. A cork borer was used to remove a central core of agar from the tube leaving a lumen into which a 4cm section of a coated catheter having an outside dimension approximating that of the lumen opening was inserted. 1.2 cc of sterile urine was introduced into the lumen before the catheter was inserted. Once the catheter was inserted, an inoculum comprising a suspension containing 2×10^5 CFU of a mixture of 50% *Escherichia coli* and 50% *Staphylococcus epidermidis* was swabbed around the upper opening of the lumen adjacent the catheter.

The culture tube was incubated at 37°C. Once in each subsequent 24 hour period over the course of the test, 0.2 cc of urine was removed from within the catheter and lumen and the lumen was supplied with a fresh quantity, .2 cc, of sterile urine, which had just been inoculated with 2×10^5 CFU of the 50% *E. coli* and 50% *Staph. epi* inoculum. At the same time, 0.01 cc of the solution removed from the lumen was tested by subculturing on a blood agar plate to determine the presence or absence of microorganisms in the liquid. In Table V below is given the number of days before growth of microorganisms was observed, either visually in the agar surrounding the lumen or in the urine samples analyzed on blood agar plates.

Comparative results between commercially coated catheters and those coated in accordance with this invention further demonstrated the significant improvement obtained; the greater the zone of inhibition, the greater the degree of suppression and cidal tendencies. Table V, below gives the results of this series of tests.

TABLE V

Antibacterial Efficacy of Urinary Catheter

<u>Drugs in Catheter Coating</u>	<u>Agar Lumen Test (Days)</u>	<u>Zone of Inhibition (mm)</u>	<u>Activity in Presence of TSB (Days)</u>
1. Silver sulfadiazine + chlorhexidine	>15 (cidal)	20	>10
2. Silver nitrate + chlorhexidine	>15 (cidal)	20	>10
3. Silver nitrate + sulfadiazine + chlorhexidine	>15 (cidal)	20	>10
4. Silver oxide (Baxter Travenol)	1 (static)	10	0
5. No drug (Control)	0	0	0

Example 3Multicoating

At times, urinary catheters or intravenous catheters coated with biomedical polyurethane and bio-active agents or silicone (with or without PLA) and bio-active agents are found to possess surface characteristics

not fully desirable. To overcome this problem, the invention further comprises the provision of a second (or more) coatings.

It has been found that a second coating applied over the biomedical polyurethane coating by spraying, dipping or otherwise, of between 0.5 and 5% of a silicone such as MDX4-4195, Dow Corning, in solution in hexane, preferably 2%, after drying, renders the coated medical device, especially a catheter, smoother in texture, with improved lubricity, without interfering with the controlled release characteristics as shown in Table VI.

TABLE VI

Retention of Antibacterial Efficacy
in Presence of TSB Culture

Drug Coated Catheter Sample	Bacterial Growth Days						
	1	2	3	4	5	6	7
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	1+	2+
4	0	0	0	0	0	0	0
5	0	0	0	0	1+	2+	4+
6	0	0	0	0	0	0	1+
7	0	0	0	0	0	0	1+
8	0	0	0	0	0	0	1+
9	0	0	0	0	0	0	1+
Control Catheter: No Antimicrobial Agent	Heavy (++)						

2cm segments of drug coated catheters (AgSD + CHA) in a biomedical polyurethane coating agent of 3% Pellethane® 2363-80AE in a solvent of THF + ethanol or DMAC + ethylacetate were coated with a second coating by applying thereto a 2% solution of MDX4-4195 in hexane. After thorough drying to remove solvent, the segments were suspended in 5ml TSB containing 10^4 *Staph. aureus* and incubated at 37°C. Every 24 hours, for seven days, the bacterial growth in the culture was measured by visual turbidity and colony counts and the catheter segment was transferred to fresh culture and the experiment repeated.

Bacterial growth was properly suppressed for seven days. In addition, the catheters possessed smoother surfaces. This multi-coating process can also use PLA in the first coating, and over a range of 0.2 to 2%, preferably 1%, in the coating vehicle with improved results.

Example 4

Coating Antimicrobial Agents and Heparin or Dextran Sulfate on I.V. Catheters

It is sometimes important that certain medical devices possess bio-activity beyond antimicrobial effects. To this end, it has been found that other bio-active agents can be incorporated into the matrices without ham-

pering the antimicrobial aspects.

As a preferred embodiment, polyurethane catheters were coated with a biomedical polyurethane coating vehicle containing 1% chlorhexidine + 1% AgSD + 0.2% heparin. The heparin imparts anti-coagulant effects to the catheter. Likewise, dextran sulfate was incorporated in the same quantities.

Table VII, below provides data showing that the addition of heparin to the coating vehicle does not interfere with antimicrobial activity of the coated device.

TABLE VII
Retention of Antibacterial Efficacy
in Heparin-Coated Catheters

	Retention of <u>Antimicrobial Activity (Days)</u> <u>With Heparin</u> <u>Without Heparin</u>	
Triple lumen catheter	6	6
Single lumen catheter	4	4

The testing was done in TSB culture as described above. The coating which was made as follows: 0.2gm of heparin was dissolved in 2-3cc of water to which 7ml of ethyl alcohol was added. 3gm of biomedical polyurethane, Pellethane® 2363-80AE, was dissolved in 75ml of THF and the heparin solution mixed therein. 1gm of chlorhexidine acetate was dissolved in 15 ml of ethanol, after which 1gm of AgSD was suspended therein. The antimicrobial agent solution was mixed with the polyurethane solution, and agitation maintained to insure a uniform suspension. The catheters were dipped in the solution, dried and tested. Coating can also be done in stages, i.e., a first coating of antimicrobial + matrix, followed by a second of heparin + matrix.

Example 5

Arterial grafts of two commercially available types were provided with an antimicrobial coating in accordance with the invention. One was an expanded polytetrafluorethylene (PTFE) sold under the Gortex® name as a reinforced expanded PTFE vascular graft 8 mm in diameter. The second was a 6 mm straight woven Dacron® arterial graft sold by Bard.

Short sections of each of these materials were coated with each of the following coating vehicles:

1. 1% PLA + 1% polyurethane + 1% CHA +
3% piperacil in 25% NEP
75% THF
2. 0.5% PLA + 0.5% polyurethane + 1%
CHA + 3% piperacil in 25% NEP
75% THF

100 ml batches of these coating vehicles were prepared by dissolving 3 gm of piperacil in 20 cc of NEP. 1 gm of CHA was separately dissolved in 5 cc of NEP. The required amount, either 1 gm or 0.5 of polyurethane was dissolved in 50 cc of THF and the same amounts of PLA were dissolved in 25 cc of THF. The four solutions were then combined and thoroughly mixed to provide the coating vehicles.

The polyurethane used was Pellethane® 2363-80AE. The PTFE sections, because of their unique structure, contain a number of cavities or interstices which require either vigorous agitation or the application of a vacuum to the section in the presence of coating vehicle to insure that the coating vehicle penetrates and permeates the graft. The woven graft requires only simple agitation in coating vehicle to provide a good coating.

Both products are then air dried.

A good adherent coating formed on the Dacron® graft. In the case of the PTFE graft, its characteristic surface refused to retain a surface coating. However, the coating composition was retained in the interstices, and, on drying, retained a coating composition having, by weight, one part biomedical polyurethane, one part PLA, one part CHA, and three parts piperacil in the case of coating 1, and .5 parts each of PLA and polyurethane, with one part CHA and three parts piperacil for coating 2.

The activity of the processed grafts are determined by the two types of bioassays described below:

Bioassay A - 2cm sections of graft are embedded in a 5% sheep's blood agar plate which was inoculated with 2×10^4 CFU *Staph. aureus*. Activity was determined by measuring the zone of inhibition. The graft sections were transferred to newly inoculated plates daily until antibacterial activity ceased.

Bioassay B - 1cm section of graft were soaked in 5cc of trypticase soy broth (TSB) which was inoculated with 10^4 CFU of *Staph. aureus*. If there was no turbidity after 24 hours incubation at 37°C, then the material was deemed to be bacteriostatic. The grafts were transferred to new TSB and inoculated daily.

Bioassay A

Group

Results

Days	Zone of Inhibition (mm)			
	<u>1</u>	<u>3</u>	<u>6</u>	<u>9</u>
PTFE (Formula 1)	23	19	16	12
PTFE (Formula 2)	29	20	16	12
Bard (Formula 1)	29	15	12	12
Bard (Formula 2)	29	15	14	11.5
Untreated Control	0			

Bioassay B

All processed groups show activity for more than 10 days.

Untreated Control showed heavy growth and turbidity after one day.

Example 6

An expanded polytetrafluorethylene (PTFE) hernia patch was impregnated with an infection-resistant material comprising silver sulfadiazine and chlorhexidine acetate in a biodegradable matrix of poly(lactic acid) using the following method.

An impregnating vehicle was prepared by mixing 0.5% chlorhexidine acetate, 0.5% silver sulfadiazine and 1% poly(lactic acid), mw 44,000, in a solvent mixture comprising 95% ethanol and THF in the proportions of 10:90. The chlorhexidine acetate and PLA are in solution in this mixture; the silver sulfadiazine is in suspension.

An expanded PTFE hernia patch, 2x2 cm and having a thickness of about 0.5 mm was soaked for 5 minutes in the impregnating vehicle prepared above, with continuous stirring to maintain a uniform suspension. The patch was then removed from the suspension, air dried for about one minute and then placed in an oven at 40°C for 24 hours.

The antibacterial efficacy of the patch was evaluated, utilizing Bioassay B described in Example 5 above. Several 1 cm² pieces were cut and soaked in TSB and kept in water bath shakers at 37°C. The TSB is changed daily and 4 pieces were removed at different intervals and tested for zone of inhibition. The results are given in the following table:

	<u>Days of Soaking</u>	<u>Zone of Inhibition (mm)</u> <u>against Staph. aureus after 1 day</u>
5	0	24
	1	22
	3	20
10	6	20

Example 715 Method of in situ Incorporation of Silver Sulfadiazine and Chlorhexidine in Hernia Patch

The interstices of a hernia patch, which is made up of expanded PTFE, are too small for a sufficient amount of silver sulfadiazine (AgSD) molecules to enter. Therefore, silver sulfadiazine is precipitated in situ by treating the patch with sodium sulfadiazine (NaSD) and silver nitrate. The following methods were used to incorporate silver sulfadiazine and chlorhexidine acetate (CHA) into the interstices of a patch.

20 1. An expanded polytetrafluorethylene (PTFE) hernia patch, 2x2 cm and having a thickness of about 0.5 cm is first soaked in:

(a) a 95% ethanol solution of 0.5% silver sulfadiazine and 0.5% chlorhexidine acetate for 2-3 minutes, removed, dried for about one minute;

25 (b) the patch is then soaked in 0.25% AgNO₃ solution for 2-3 minutes, removed and air dried. The patch is then placed in an oven at 40°C for 24 hours.

2. The procedure is the same as in 1, but the first solution contains 0.4% sodium sulfadiazine, 0.5% chlorhexidine acetate, and 1% PLA, mw 44,000, in a solvent comprising a 95% ethanol:THF mixture (10:90). In an alternative to both the 1 and 2 methods, the first dipping step was done in AgNO₃ solution and then in the mixture of sodium sulfadiazine and chlorhexidine acetate.

Evaluation of Antibacterial Efficacy of Patches Coated by this Process

35 Following the bioassay method of Example 6, several 1 cm² pieces were cut and soaked in TSB and kept in water bath shakers. The TSB was changed daily and 4 pieces were removed at different intervals and tested for zone of inhibition.

	<u>Coating Procedure</u>	<u>Zone of Inhibition (Days)</u>		
		<u>1</u>	<u>3</u>	<u>6</u>
40	<u>Method A</u>			
	NaSD + CHA + AgNO ₃	23	21	20
	AgNO ₃ + NaSD + CHA	22	21	20
45	<u>Method B</u>			
	NaSD + CHA + PLA + AgNO ₃	22	20	19
	AgNO ₃ + NaSD + CHA + PLA	22	20	19

Example 8

55 A coating vehicle for use in accordance with the present invention was prepared as follows:
1 gm of chlorhexidine acetate (CHA) was added to 5 cc of N-ethyl-2-pyrrolidone (NEP). The mixture was heated to 50-60°C and agitated in a Vortex® stirrer until the CHA dissolved.

10 cc tetrahydrofuran (THF) was then added to the CHA solution in NEP and the mixture thoroughly agitated to form a uniform solution.

3 gm of Pellethane® 2363-80AE of the Dow Chemical Co. was added to 50 cc of THF. The mixture was warmed to about the boiling point of THF, 65-70°C, and stirring with a Vortex® stirrer was continued until the polyurethane was dissolved.

1 gm of silver sulfadiazine (AgSD) micronized powder was suspended in 35 cc of THF and vigorously agitated in a Vortex® stirrer to form a uniform suspension. The CHA solution in NEP and THF prepared above was then combined with the polyurethane solution and agitated to form a clear solution. As a last step in preparing the coating vehicle, the AgSD suspension in THF was added and the entire mixture agitated to maintain a uniform suspension. Thus was provided a coating vehicle containing 1% CHA and 1% AgSD as antimicrobial agents, together with 3% of the biomedical polyurethane. The solvent in this case was a mixture of solvents comprising 5% NEP and 95% THF. The CHA was in solution in the coating vehicle, while the AgSD was in uniform suspension.

The coating vehicle prepared above was used to coat an I.V. catheter fabricated of Pellethane® 2363-90A. The catheter was dipped in the coating vehicle while the vehicle was being continuously agitated to insure a uniform suspension. The coated catheter was then dried. A tightly adherent coating on the catheter was thus provided.

Example 9

Synergism of Silver Sulfadiazine (AgSD) and Chlorhexidine (CHA)

The results of experiments described below indicate that coating silver salts, preferably sulfadiazine, and chlorhexidine or its salts onto medical devices imparts prolonged antibacterial activity. In addition, *in vitro* studies show that chlorhexidine exhibits a synergistic effect when combined with silver sulfadiazine and thus increases the antimicrobial spectrum. AgSD + CHA also kills 99.9% of the bacterial population faster than chlorhexidine alone which is important for its use in medical gloves and condoms. Furthermore, when wound dressings (Epilock® dressings) coated with silver sulfadiazine and chlorhexidine were tested for zone of inhibition against a mixed culture of *Staph. aureus* and *Ps. aeruginosa*, a synergistic effect was observed.

Analytical Procedures for Determinating the Drug Content and Rate of Release from Devices

Determination of silver (Ag), sulfadiazine (SD) and chlorhexidine acetate (CHA) values is performed as follows:

Silver and SD

The devices (catheters) were coated with radioactive silver sulfadiazine (¹¹⁰AgSD) and after measuring the initial radioactivity they were suspended in culture media or saline. The catheters were transferred daily to fresh media or saline and the radioactivity remaining in the catheter segments were measured using a Nuclear Chicago 1185 automated gamma counter. The amount of SD released was measured by determining the SD content of the media using a calorimetric method (Bratton-Marshall Test).

Initial levels of SD in the catheters were determined by extracting the SD from the catheters with 0.2 molar nitric acid.

CHA

CHA levels are determined spectrophotometrically (231nm and 254nm) using a Hitachi® 2000 double beam UV/VIS system. Initial levels were measured by extracting the CHA from the catheter using warm ethanol. The CHA released into the media was also measured spectrophotometrically. These spectrophotometric levels were corroborated by bioassay such as zone of inhibition tests.

In vitro Studies

Different concentrations of silver sulfadiazine or chlorhexidine were added to mixed cultures of *Ps. aeruginosa* and *Staph. aureus* (10⁵ CFU each organism) in 2 ml trypticase soy broth (TSB) and incubated along with control cultures. 0.1 ml aliquots were removed from these cultures and diluted to 10 ml (1 to 100 dilution) at 10 minutes, 20 minutes and 40 minutes. 0.2 ml of these diluted samples were subcultured on blood agar

plates and colony counts were made 24 hours post incubation. The results are given the following Table VIII.

TABLE VIII

Bacterial Inhibition

Antimicrobial Agent	Concentration (μ mole/2 ml)	Colony Forming Units (CFU)		
None	0	$\frac{10^6}{>10^6}$ (S&P)	$\frac{20^6}{>10^6}$ (S&P)	$\frac{40 \text{ minute}}{>10^6}$ (S&P)
AgSD	1.0	2×10^5 (S&P)	1×10^5 (S&P)	1.2×10^5 (S&P)
CHA	1.0	1×10^3 (S)	0	0
AgSD + CHA	1.0 + 1.0	0	0	0
AgSD	0.5	$>10^6$ (S&P)	$>10^6$ (S&P)	$>10^6$ (S&P)
CHA	0.5	1×10^5 (S)	3.7×10^4 (S)	2×10^2 (S)
AgSD + CHA	0.5 + 0.5	0	0	0

S&P = Staph. aureus and Ps. aeruginosa
 S = Staph. aureus

The results show:

1. chlorhexidine acts rapidly, and by 20 minutes kills the organisms present;
2. silver sulfadiazine exhibits steady and prolonged suppression of growth (also see the example relating to wound dressings below); and
3. AgSD + CHA demonstrate a marked improvement over the individual results as there is even a more rapid kill (10 minutes), and prolonged suppression.

The results clearly show a fast and prolonged and synergistic antibacterial activity for the combination of AgSD + CHA, exhibiting far superior results than by using each such antimicrobial agent alone.

Example 10

Synergistic results are also found when other silver salts are combined with chlorhexidine, as shown in Table IX, below.

TABLE IX

**Synergistic Effect of Silver Compounds
and Chlorhexidine against Staph. aureus, in vitro**

	<u>Drug Concentration in Culture</u>	<u>Colony Count (Minutes)</u>	
		<u>20</u>	<u>50</u>
10	100µg silver sulfadiazine	9,500	8,000
	100µg silver oxide	7,500	8,000
15	100µg silver carbonate	9,200	6,000
	100µg chlorhexidine acetate	6,250	4,000
20	50µg silver sulfadiazine + 50µg chlorhexidine acetate	4,800	0
	50µg silver oxide + 50µg chlorhexidine acetate	3,700	0
25	50µg silver carbonate + 50µg chlorhexidine acetate	4,300	0
	100µg silver nitrate	10,500	11,000
30	100µg chlorhexidine, water insoluble	6,000	3,000
	50µg silver nitrate + 50µg chlorhexidine, water insoluble	100	0
35	CONTROL	16,000	15,000

For Table IX, 3 ml of TSB culture of Staph. aureus (10^4 CFU/ml) containing the drug were incubated for one hour at 37°C and the colony counts measured. The results achieved further show the synergistic interaction between silver salts and chlorhexidine salts in causing complete suppression of growth by 60 minutes, whereas each anti-bacterial agent, alone, showed only partial suppression.

Example 11

Methods for the Preparation of Coated Medical Devices and Evaluation of Antibacterial Activity

Certain medical devices are comprised of materials not fully compatible with biomedical polyurethane as a coating vehicle, requiring, for compatible matrices, the use of a biomedical silicone, with or without a biodegradable polymer such as poly(lactic acid) (PLA).

Method A

Chlorhexidine diacetate is mixed uniformly in 1% to 10%, preferably 5%, silicone solution in ethyl acetate, or silicone solution containing .2 to 2%, preferably 0.5% or 1% poly(lactic acid), molecular weight 2000. The medical device is dipped for 10 seconds in this suspension which is kept at room temperature. The silicone used was Silastic® Medical Adhesive Silicone Type A.

Method B

0.5 to 10% chlorhexidine diacetate is mixed uniformly in 1% PLA solution (equal amounts of 2,000, 44,000, 100,000 and 300,000 molecular weight PLA) in ethyl acetate. This antimicrobial suspension is kept at 50°C in a water bath and mixed continuously. The medical device to be coated is dipped for one minute in this suspension, removed and dried.

In both of the above methods, other antimicrobial agents can also be used either singly or in combination as shown below.

Coating of Latex Gloves

The fingers of latex medical gloves were washed, dried and dip-coated with (a) chlorhexidine acetate (CHA), (b) CHA and silver sulfadiazine (AgSD), and (c) AgSD using antimicrobial suspensions prepared by Method A above. The silicone used in this test was a mixture of equal parts by weight of Silastic® Medical Adhesive Silicone Type A, and MX-4-4159, a fluid comprising equal parts of an active polydimethyl siloxane and a solvent thereof comprising mixed aliphatic and isopropanol solvents. The PLA employed was a poly(L-lactic acid) procured from Polysciences, Inc., Warrington, Pennsylvania, having various molecular weights. PLA-2000 has a molecular weight of 2000. The suspension had the following composition:

1. 10% CHA + 10% silicone + 0.5% PLA-2000
2. 5% CHA + 5% AgSD + 10% silicone + 0.5% PLA-2000
3. 10% silver sulfadiazine + 10% silicone + 0.5% PLA-2000

The antibacterial efficacy was tested against a mixed culture of *Pseudomonas aeruginosa* and *Staphylococcus aureus* having 10⁴ CFU of each per 2 ml of culture.

The coated fingers were suspended in culture tubes and 2 ml of 5% bovine albumin solution containing the mixed bacterial culture were added to it and incubated at 37°C. The rate of killing was determined by taking aliquots at 10, 20 and 40 minutes and subculturing on blood agar plates for colony counts. The results are given in Table X below.

TABLE X

Colony Counts of *Staph. aureus*
and *Ps. aeruginosa*
(Colony Forming Units - CFU/2 ml Culture)

<u>Antimicrobial Agent on Gloves</u>	<u>10 Minutes</u>		<u>20 Minutes</u>		<u>40 Minutes</u>	
	<u>Staph. aureus</u>	<u>Ps. aer.</u>	<u>Staph. aureus</u>	<u>Ps. aer.</u>	<u>Staph. aureus</u>	<u>Ps. aer.</u>
CHA	8x10 ³	0	2x10 ³	0	0	0
CHA + AgSD	4x10 ³	0	0	0	0	0
AgSD ₃ 5x10 ³	1x10 ⁴	1.2x10 ⁴	5x10 ³	8x10 ³	4x10 ³	
None ₄ (Contrgl) 2x10 ⁴ 8x10 ³		1x10 ⁴	1x10 ⁴	1x10 ⁴	8x10 ³	

These results demonstrate improved and sustained suppression of bacterial growth when using the combination of CHA + AgSD on gloves.

Example 12Coating of Urinary Catheters and Evaluation of Antibacterial Activity

Using the methods described in A and B in Example 11 above, latex urinary catheters were coated with a coating vehicle containing Silastic® Medical Adhesive Silicone Type A in Method A and PLA in Method B.

both having various amounts of chlorhexidine and silver sulfadiazine and 2.0 cm segments were soaked in either 5 ml trypticase soy broth (TSB) or 5 ml urine inoculated with a mixture of 10^4 organisms of *Staph. epi* and *E. coli*. After 24 hours of incubation at 37°C, the media was subcultured to quantitatively determine bacterial levels. The segments were then transferred to fresh media which was re-inoculated. This procedure was continued until the urinary catheter segments no longer presented antibacterial activity. The results, showing significant retention of bio-active material are given in Table XI below.

TABLE XI
Retention of Antibacterial
Activity of Coated Urinary Catheters

Antimicrobial Agent on Urinary Catheters	% Anti- Microbial in coating Solution	Retention (Days)			Nutrient Agar Plate
		In Pres- ence of Urine	In Pres- ence of TSB		
Method A - CHA + AgSD	5+5	3	3		>7
Method A - None (Control)	0	0	0		0
Method B - CHA + AgSD	5+5	3	3		6
Method B - None (Control)	0	0	0		0
CHA = chlorhexidine acetate					
AgSD = silver sulfadiazine					

Example 13

Multicoating

At times, urinary catheters or intravenous catheters coated with biomedical polyurethane and bio-active agents or silicone (with or without PLA) and bio-active agents are found to possess surface characteristics not fully desirable. To overcome this problem, the invention further comprises the provision of a second (or more) coatings.

It has been found that a second coating applied over the biomedical polyurethane coating by spraying, dipping or otherwise, of between 0.5 to 5% of a silicone fluid such as the MDX4-4195 described in Example 11 in solution in hexane, preferably 2%, after drying, renders the coated medical device, especially a catheter, smoother in texture, with improved lubricity and improved retention characteristics, as shown in Table XII.

TABLE XIIRetention of Antibacterial Efficacy
in Presence of TSB Culture

5

	<u>Drug Coated Catheter Sample</u>	<u>Bacterial Growth Days</u>						
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>
10	<u>MDX Coating</u>							
	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
15	3	0	0	0	0	0	1+	2+
	4	0	0	0	0	0	0	0
20	5	0	0	0	0	1+	2+	4+
	6	0	0	0	0	0	0	1+
	7	0	0	0	0	0	0	1+
25	8	0	0	0	0	0	0	1+
	9	0	0	0	0	0	0	1+
30	<u>No MDX Coating</u>							
	1	0	0	0	0	0	1+	
	2	0	0	0	0	1+	1+	
35	3	0	0	0	0	1+	1+	
	4	0	0	0	0	1+	1+	
40	5	0	0	0	0	1+	1+	
	6	0	0	0	0	0	1+	
45	Control Catheter No Antimicrobial Agent	Heavy (++)						

2 cm segments of drug coated catheters (AgSD + CHA) in a biomedical polyurethane coating agent of 3% Pellethane® 2363-80AE in a solvent of THF + ethanol or DMAC + ethylacetate were coated with a second coating by applying

hereto a 2% solution of MDX4-4195 in hexane. After thorough drying to remove solvent, the segments were suspended in 5 ml TSB containing 10^4 *Staph. aureus* and incubated at 37°C. Every 24 hours, for seven days, the bacterial growth in the culture was measured by visual turbidity and colony counts and the catheter segment was transferred to fresh culture and the experiment repeated.

Bacterial growth was properly suppressed for seven days. In addition, the catheters possessed smoother surfaces. This multicasting process can also use PLA in the first coating, and over a range of 0.2 to 2%, preferably 1%, in the coating vehicle with improved results.

Example 14Coating Antimicrobial Agents and Heparin or Dextran Sulfate on I.V. Catheters

It is sometimes important that certain medical devices possess bio-activity beyond antimicrobial effects. To this end, it has been found that other bio-active agents can be incorporated into the matrices without hampering the antimicrobial aspects.

As a preferred embodiment, polyurethane catheters were coated with a biomedical polyurethane coating vehicle containing 1% chlorhexidine + 1% AgSD + 0.2% heparin. The heparin imparts anti-coagulant effects to the catheter. Likewise, dextran sulfate was incorporated in the same quantities.

Table XIII, below provides data showing that the addition of heparin to the coating vehicle does not interfere with antimicrobial activity of the coated device.

TABLE XIII

Retention of Antibacterial Efficacy
in Heparin-Coated Catheters

	<u>Retention of</u> <u>Antimicrobial Activity (Days)</u>	
	<u>With Heparin</u>	<u>Without Heparin</u>
Triple lumen catheter	6	6
Single lumen catheter	4	4

The testing was done in TSB culture as described above. The coating which was made as follows: 0.2 gm of heparin was dissolved in 2-3 cc of water to which 7 ml of ethyl alcohol was added. 3 gm of biomedical polyurethane, Pellethane® 2363-80AE, was dissolved in 75 ml of THF and the heparin solution mixed therein. 1 gm of chlorhexidine acetate was dissolved in 15 ml of ethanol, after which 1 gm of AgSD was suspended therein. The antimicrobial agent solution was mixed with the polyurethane solution, and agitation maintained to insure a uniform suspension. The catheters were dipped in the solution, dried and tested. Coating can also be done in stages, i.e., a first coating of antimicrobial + matrix, followed by a second of heparin + matrix.

Example 15Coating of Wound Dressings

Johnson and Johnson gauze dressings and Epilock® dressings manufactured by Dermalock Medical Corporation were coated with antimicrobial agents. These coated dressings were prepared using methods (a) and (b) above. The zone of inhibition was tested against a mixture of *Ps. aeruginosa* and *Staph. aureus* cultures on nutrient agar plate.

TABLE XIV-AAntibacterial Activity of
Johnson and Johnson Dressings

<u>Antimicrobial Agent in Dressings</u>	<u>% Antimicrobial Agent in Coating Solution</u>	<u>Zone of Inhibition (mm)</u>	
		<u>1 Day</u>	<u>2 Day</u>
Method A - CHA + AgSD	5-5	25	20
None (Control)	0	0	0

TABLE XIV-BAntibacterial Activity of
Spillock® Dressings

<u>Antimicrobial Agent in Dressings</u>	<u>% Antimicrobial Agent in Coating Solution</u>	<u>Zone of Inhibition (mm)</u>				
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5 Days</u>
Method A - CHA + AgSD	5-5	34	45	43	27	34
Method B - CHA + AgSD	5-5	38	28	37	30	25
None (Control)	0	0	0	0	0	0

These results demonstrate the improvement in using the synergistic combination, as well as the general efficacy of the process. Wound dressings may also be provided with an adhesive on one side (to attach to the wound). In such cases, the invention further comprises seven methods of application of the antimicrobial agent:

1. Suspending the antimicrobial agents, preferably silver sulfadiazine and chlorhexidine in the quantities of 1-5% total, in a carrier that evaporates but does not solubilize the adhesive, instead leaving the adhesive intact, e.g., an alcohol, and spraying the agent-containing carrier upon the dressing, or dipping the dressing into the agent-containing carrier solution.
2. Placing the antimicrobial agents in a solution containing silicone or polyurethane (preferably 1%) and a carrier (preferably ethyl acetate, THF or H₂O) and spraying it upon the dressing, or dipping the dressing into it.
3. Applying powdered antimicrobial agents (preferably silver sulfadiazine and chlorhexidine) to the adhesive in microlayers that do not eliminate adhesion.
4. Admixing powdered antimicrobial agents with adhesive prior to application.
5. Adding a biodegradable material containing antimicrobial agents to the adhesive to provide controlled-release through degradation.
6. Providing spots containing antimicrobial agents, surrounded by adhesive.
7. Providing a biodegradable or nonbiodegradable adhesive composition containing antimicrobial agents.

Example 16Method of Coating Antimicrobial Agents on the Surface of Latex Gloves During Automated Manufacturing Process

The invention is especially useful in the automated manufacturing of gloves. There are two methods found useful in the coating of the combination of chlorhexidine and silver sulfadiazine.

Method 1

Latex gloves are typically manufactured by (1) dipping a form in molten latex, (2) removing the latex form and transferring it to a dryer, (3) removing the form with attached glove from the dryer and immediately spraying it with a dusting powder, as it cools. A suspension of silver sulfadiazine in alcohol or water in an aqueous silicone latex emulsion (1-5% by volume) + chlorhexidine (1-5% + dusting powder (2-10%)) is sprayed on the gloves as the gloves are dispensed from the dryer at 120°C. At this temperature, the antimicrobial agents and the dusting powder particles adhere well to the soft and/or semi-molten surfaces of the gloves. The antimicrobial activity is not in any way altered as a consequence of this process, because of the falling temperature of the gloves, as they cool. This is a preferred procedure in cases where presence of other organic solvents in the coating process is a concern to the manufacturer.

Method 2

Sterile corn starch-based dusting powder is admixed with silver sulfadiazine (1-5% by weight) and chlorhexidine (1-5% by weight) in powdered form, and the mixture is sprayed on the gloves as they are dispensed from the dryer at 120°C, and start to cool. The dusting powder with enhanced antimicrobial activity remains with the gloves.

Example 17Preparation of Infection-Resistant Devices with Silver Sulfadiazine and Chlorhexidine Using a Mixture of Silicones as the Polymeric Coating Agent

In order to obtain a coating which is lubricious, adheres well to the catheter and also releases the drug in a controlled dosing manner, a mixture of Silastic® Medical Adhesive Type A, a polydimethyl siloxane, and MDX-4-4159, a fluid silicone comprising equal parts of an amino functional polydimethyl siloxane copolymer and a mixed aliphatic and isopropanol solvent were used as the polymeric coating agents. Silastic® Medical Adhesive Silicone Type A alone forms an undesirable surface, while the MDX-4-4159 alone does not form an adherent film on the surface. However, use of a mixture of these two silicones in 1:1 proportions gives a coating vehicle which forms a film with the desired biocompatible characteristics. The Silastic® functions as the bonding agent whereas the MDX-4-4159 imparts lubricity to the surface. In addition, the MDX-4-4159 prolongs the release of the antimicrobial agent.

The coating agent was prepared by dispersing 2.5ml of Silastic® Medical Adhesive Type A in 55ml of THF to which 2.5 ml of MDX-4-4159 is added. 4 g of AgSD are suspended in 30ml and 2g of CHA are dissolved in 10ml of ethanol. The AgSD suspension is mixed with the silicone dispersions and finally the CHA solution is added dropwise while the preparation is agitated. Either 5% NEP or 5% DMAc can be substituted for ethanol in the above formulation.

The coating agent prepared above was used to apply a coating on catheters fabricated from silicone, polyurethane and latex substrates. The coatings were applied by dipping and drying, as described in Example 2. Results are given in Table XV below.

TABLE XV

Antibacterial Efficacy of Polyurethane
I.V. Catheters and Latex or Silicone Urinary
Catheters Coated with A Silicone Matrix

Catheter Type	Drug in Catheter	Days of Activity*
Polyurethane I.V.	AgSD + CHA	4
Latex urinary	AgSD + CHA	4
Silicone urinary	AgSD + CHA	4

* Determined via Bioassay A. Inoculum used to assay urinary catheter is a 10^4 CFU of a 1:1 mixture of Staph. ep. and E. coli; 10^4 CFU of Staph. aureus is used to challenge the I.V. catheter.

Example 18

Silver sulfadiazine and chlorhexidine acetate were added over a range of proportions to cultures of Staph. aureus containing 10^5 colony forming units (CFU) in 2 ml trypticase soy broth (TSB) and the cultures were incubated along with control cultures at 37°C. 0.1 ml aliquots were removed from these cultures and diluted to 10 ml, a 1:100 dilution after one hour. 0.2 ml of these diluted samples were subcultured on blood agar plates and colony counts were made 24 hours post incubation. The results are given in the following Table XVI.

TABLE XVI

Synergism of Different Combinations
of Silver Sulfadiazine (AgSD)
and Chlorhexidine (CHA) against Staph. aureus

Concentration µg/2 ml <u>AgSD + CHA</u>		Bacterial Inhibition Colony Forming Units <u>After 1 Hour</u>
0	100µg	650
25µg	75µg	100
50µg	50µg	150
75µg	25µg	100
87.5µg	12.5µg	150
100µg	0	3,100
0	0	4,100

Example 19Coating of Latex Gloves

The fingers of latex gloves were washed and dried. They were then sprayed with a fine mist spray of a coating solution to provide a uniform coating of solution on the glove surface, sufficient to provide complete wetting thereof without runoff. The coating solutions were prepared by dissolving 1% Silastic® Medical Adhesive Type A and 1% of the silicone MDX4-4159 in ethyl acetate, followed by dissolving and dispersing the chlorhexidine acetate and silver sulfadiazine, therein. The coating was air dried for 24 hours and the gloves tested using the following test:

Treated glove fingers were draped over the tops of culture tubes with the treated side with sprayed on coating forming the inside on the cup shape. Then 3.0 ml of TSB containing 10^4 colony forming units of Staph. aureus was dispensed in each finger and all placed in a water bath shaker at 37°C. Samples were removed at 15 minutes, 1 hour, 2 hours, and 4 hours, diluted 1-10, and the solution placed on blood agar in 2.0 ml amounts.

The results of the test are summarized in the following Table XVII.

TABLE XVII

Antibacterial Efficacy of Drug Coated
Gloves against Staph. aureus

Drug in Coating Solution	15 min	1 hour	2 hours	4 hours
None (Control)	12,000	15,000	20,000	50,000
Silver Sulfadiazine (1%)	0	0	0	0
- Chlorhexidine (1%)	0	0	0	0

It is noted that the gloves coated according to this procedure were flexible and met all other requirements for high quality latex gloves.

Example 20

The fingers of latex gloves were washed, dried, and sprayed with a fine mist of a coating solution to provide a uniform coating of solution on the glove surface, sufficient to provide a complete wetting thereof without runoff. The coating solutions were prepared by dissolving 1% Silastic® Medical Adhesive Type A and 1% of the silicone MDX4-4159 in ethyl acetate, followed by dissolving or dispersing the chlorhexidine acetate and silver sulfadiazine therein. The coating was air dried for 24 hours and the gloves tested using the following test:

Treated glove fingers were draped over the tops of culture tubes with the treated side with sprayed on coating forming the inside on the cup shape. Then 3.0 ml of TSB containing 10^3 colony forming units of Candida albicans was dispensed in each finger and all placed in a water bath shaker at 37°C. Samples were removed at 15 minutes, 1 hour, 2 hours, and 4 hours. They were diluted 1-10 and plated on blood agar in 2.0 ml amounts.

The results of the test are summarized in the following Table XVIII.

TABLE XVIIIAntibacterial Efficacy of Drug Coated Gloves
against Candida albicans

<u>Drug in Coating Solution</u>	<u>Colony Counts in Culture</u>			
	<u>15 min.</u>	<u>1 hour</u>	<u>2 hours</u>	<u>4 hours</u>
None (Control)	1,400	2,000	4,000	5,000
Silver sulfadiazine (1%) + Chlorhexidine (1%)	0	0	0	0

As in Example 20, the gloves coated according to this procedure were flexible and met all requirements for high quality latex gloves.

Example 21

The fingers of latex gloves were washed and dried. They were then sprayed with a fine mist spray of the coating solution in runs 1-3 below to provide a uniform coating of solution on the glove surface, sufficient to provide a complete wetting without runoff, after which the gloves were dried for 24 hours. In run 4, the powder was blown on to the glove to form a uniform coating.

The coating solutions were prepared having the following ingredients:

1. 1% MDX4-4159 + 1% Silastic® Medical Adhesive Type A + 1% CHA + 1% AgSD + 2% starch-based dusting powder in ethyl acetate.
2. 1% CHA + 1% AgSD + 2% dusting powder in ethanol.
3. 1% chlorhexidine gluconate (CHG) + 1% AgSD + 2% dusting powder in ethanol.
4. A mixture of CHA + AgSD + dusting powder in equal weight ratios.

The coated gloves were tested, following the procedure set forth in Example 16 above. The results are given in Table XIX.

TABLE XIXAntibacterial Efficacy of Drug Coated
Gloves against Staph. aureus

<u>Coating Solution</u>	<u>Colony Counts in Culture</u>	
	<u>15 min.</u>	<u>1 hour</u>
1	0	0
2	0	0
3	0	0
4	0	0
None (Control)	12,000	15,000

It is noted that other medical gloves, including surgical and examination gloves, fabricated from other materials such as polyurethane, polyethylene, polypropylene, and polyvinyl acetate, may be coated following the process of this invention.

It is further noted that in both the dry powder process and the so-called wet powder process using a vehicle such as ethanol, the antimicrobial powders and dusting powders may be applied separately, and in any se-

quence.

Example 22

This example illustrates the coating of medical gloves with a coating composition containing an aqueous silicone emulsion.

15 grams of starch-based dusting powder is suspended in 50 ml of deionized water. The suspension is then mixed with 44.5 ml of deionized water in which 2 grams of micronized silver sulfadiazine is suspended. To this mixture is added .5 cc of L.E. 46, a silicone emulsion containing 35% dimethyl siloxane, sold by Dow Corning Company. Finally, 5 cc of a 20% chlorhexidine gluconate in water is added and the mixture stirred to maintain a uniform suspension.

Washed latex glove fingers are dipped into the mixture and air dried for one minute to provide an adherent, infection-resistant, coating.

Example 23

Latex urinary catheters were provided with coatings including a series of antimicrobial agents. A coating solution was prepared containing 6% Dow Pellethane® 80AE in solvent comprising 5% NEP and 95% THF. The catheters were dipped in the solution to provide a uniform coating, and dried for 24 hours to remove the solvent. The silver salt was at a 2% level, as was the CHA. All silver salts were very finely divided, either by grinding in a mortar and pestle, or by purchase of micronized grade materials. Three 1 cm segments of each catheter were placed in the center of blood agar plates seeded with 10^4 CFU of a 1:1 mixture of *Staph. epi* and *E. coli*, one section to each plate, and the zone of inhibition was measured after incubation at 37°C for 24 hours. The results are given in the following Table XX.

TABLE XX

Antibacterial Efficacy of Drug Coated
Urinary Catheters against *Staph. ep.* and *S. coli*

Drug on Catheter	Zone of Inhibition (mm), Days						
	Days	1	2	3	4	5	6
Silver acetate + CHA	20	21	14	14	12	12	
Silver benzoate + CHA	18	20	12	13	13	14	
Silver carbonate - CHA	20	23	19	12	13	13	
Silver iodate - CHA	18	20	15	14	14	15	
Silver laurate + CHA	22	24	19	18	18	17	
Silver protein - CHA	26	26	15	16	16	17	
Silver palmitate + CHA	26	26	23	18	18	18	
Silver chloride - CHA	20	15	14	15	15	15	
Silver oxide - CHA	20	25	15	14	15	15	
Silver sulfadiazine - CHA	20	15	15	15	16	16	
Silver tannate + CHA	20	-*	-	-	-	-	

* Experiment discontinued after 1 day because of poor quality coating.

Example 24

I.V. catheters fabricated of Pellethane® 2363-90A were provided with coatings including a series of anti-microbial agents. A coating solution was prepared containing 6% Dow Pellethane® 2363-80AE and the drug in a solvent comprising 5% N-ethyl-2-pyrrolidone (NEP) and 95% tetrahydrofuran (THF). The Ag salt was used of 2%. The catheters were dipped in the solution to provide a uniform coating on the device, and thereafter allowed to dry for 24 hours to remove the solvent.

Three 1 cm segments of each catheter were placed in the center of blood agar plates seeded with 10^4 CFU of *Staph. aureus*, one section to a plate, and the zone of inhibition was measured after 24 hours at 37°C. Results, expressed as the average of 3 determinations, are given in the following Table XXI.

TABLE XXI

Antibacterial Efficacy of Drug Coated
I.V. Catheters against Staph. aureus

	<u>Drug on Catheter</u>	<u>Zone of Inhibition (mm)</u>				
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
10	Silver acetate + CHA	18	11	11	14	11
	Silver benzoate + CHA	18	11	25	13	13
15	Silver carbonate + CHA	17	12	17	13	13
	Silver iodate + CHA	18	12	17	12	8
20	Silver laurate + CHA	25	13	21	15	11
	Silver protein + CHA	19	11	12	12	9
25	Silver chloride + CHA	18	11	17	13	13
	Silver oxide + CHA	19	10	13	12	14
30	Silver sulfadiazine + CHA	16	11	15	14	13
35	Silver tannate + CHA	19	-	-	-	-*
	* Experiment discontinued after 1 day because of poor quality coating.					

40 Example 25

I.V. catheters fabricated of Pellethane® 2363-90A were provided with coatings including a series of anti-microbial agents. A coating solution was prepared containing 6% Dow Pellethane® 2363-80AE and the drug in a solvent comprising 5% N-ethyl-2-pyrrolidone (NEP) and 95% tetrahydrofuran (THF). The Ag was used at a level of 2%. The catheters were dipped in the solution to provide a uniform coating on the device and there-
after allowed to dry for 24 hours to remove the solvent.

1 cm segments of each catheter were soaked in TSB and incubated at 37°C in a water bath shaker. At intervals of 0, 3, 6, 9, and 12 days, 3 segments were recovered from each group, placed in the center of blood agar plates seeded with 10⁴ CFU of Staph. aureus, one section to a plate, and the zone of inhibition was measured after 24 hours at 37°C. Results, expressed as an average of 3 determinations, are given in the following Table XXII.

TABLE XXII

Antibacterial Efficacy of Drug Coated
I.V. Catheters against Staph. aureus
in Presence of Trypticase Soy Broth

	<u>Drug on Catheter</u>	<u>Zone of Inhibition (mm)</u>			
		<u>3</u>	<u>6</u>	<u>9</u>	<u>12</u>
	Silver acetate + CHA	15	11	12	10
	Silver benzoate + CHA	13	10	12	12
	Silver carbonate + CHA	14	13	13	12
	Silver iodate + CHA	15	15	10	10
	Silver laurate + CHA	26	15	15	15
	Silver protein + CHA	15	12	15	15
	Silver palmitate + CHA	26	15	15	17
	Silver chloride - CHA	20	13	13	14
	Silver oxide + CHA	13	13	12	12
	Silver sulfadiazine + CHA	19	14	12	12
	Cuprous oxide	4	0	0	0

Example 26

I.V. catheters fabricated of Pellethane® 2363-90A were provided with coatings incorporating a series of antimicrobial agents. A coating solution was prepared containing 3% Dow Pellethane® 2363-80AE and the drug in a solvent comprising 5% N-ethyl-2-pyrrolidone (NEP) and 95% tetrahydrofuran (THF). The AgSD was micronized; the Ag carbonate was ground thoroughly in mortar and pestle to very fine particle size. The catheters were dipped in the solution to provide a uniform coating on the device and thereafter allowed to dry to remove the solvent.

1 cm segments of each catheter were treated and tested according to the procedure set forth in Example 26. The results obtained, expressed as maximum period of retention of activity, are given in Table XXIII below.

TABLE XXIII

**Retention of Antibacterial Efficacy of
Different Drug Coated Catheters (Polyurethane I.V.)
in TSB Culture (10^6 Staph. aureus)**

<u>Drugs in Coating Solution</u>	<u>Days of Activity Retained</u>
None	0
AgSD + CEA (1% + 1%)	5
Ag Carbonate + CEA (1% + 1%)	5

It is to be understood that the above-described embodiments are illustrative of the application of the principles of the invention. Numerous other arrangements, processes, or compositions may be devised by those skilled in the art without departing from the spirit and scope of the invention.

Claims

- A method of preparing an infection-resistant surface, characterized by preparing a coating vehicle by dispersing a matrix-forming polymeric material selected from the group consisting of biomedical polyurethane, biomedical silicones, biodegradable polymers and combinations thereof, in at least one solvent therefor, incorporating an antimicrobial agent comprising a silver salt and a biguanide in the coating vehicle to form a coating composition, coating the surface with the coating composition, and drying the coating.
- The method of Claim 1, characterized in that the matrix-forming polymeric material is biomedical polyurethane preferably at a concentration in the range of 1 to 10%.
- The method of Claim 1, characterized in that the matrix-forming polymeric material is a mixture of biomedical silicone and a biodegradable polymer, preferably poly(lactic acid) at a concentration in the range of 0.2 to 2%.
- The method of Claim 1, characterized in that the matrix-forming polymeric material is a mixture of biomedical silicone and biomedical polyurethane.
- The method of any of Claims 1 to 4, characterized in that the solvent is selected from the group consisting of acetic acid, methyl acetate, dimethylacetamide, ethyl 2-pyrrolidone, N-(2-hydroxyethyl)-2-pyrrolidone, N-cyclohexyl-2-pyrrolidone, and combinations thereof.
- The method according to any preceding Claim, characterized in that said silver salt is selected from the group consisting of silver acetate, silver benzoate, silver carbonate, silver iodate, silver iodide, silver lactate, silver laurate, silver nitrate, silver oxide, silver palmitate, silver protein, and silver sulfadiazine.
- The method according to any preceding Claim, characterized in that the biguanide is a chlorhexidine salt and is preferably selected from the group consisting of chlorhexidine, acetate, chlorhexidine gluconate, chlorhexidine hydrochloride, and chlorhexidine sulfate.
- The method according to any one of Claims 1 to 5, characterized in that the antimicrobial agent is a combination of silver sulfadiazine and a salt of chlorhexidine, preferably chlorhexidine acetate.
- The method according to any preceding Claim, characterized in that the surface is a surface of a medical

device such as a catheter, contraceptive, a condom, a medical glove, a wound dressing, a wound clip, an orthopaedic implant, a suture, an arterial graft, or a hernia patch.

10. The method according to any one of Claims 1 to 8, characterized in that said surface is one intended to contact health care patients such as a surface of a bed pan, a table top, a patient bed, the surface of a surgical apparatus, or an operating room surface.
11. The method of any preceding Claim, characterized in that at least one antimicrobial agent is dissolved or suspended in the coating vehicle.
12. The method of any of Claims 1 to 10, characterized in that at least one antimicrobial agent is dissolved in a solvent which is miscible with the solvent for the matrix-forming polymeric material and which is subsequently incorporated into the coating vehicle.
13. A method of preparing an infection-resistant surface, characterized by preparing a first coating vehicle by dispersing a biomedical polyurethane in a solvent therefor, and optionally from 0.2 to 2% polylactic acid, and incorporating therein an antimicrobial agent comprising a silver salt and a biguanide; preparing a second coating vehicle by dispersing a biomedical silicone in a solvent therefor preferably at a concentration of 0.5 to 5%; applying said first coating vehicle to the surface and allowing it to form an adherent first coating; and applying said second coating over said first coating to form a second coating adherent to said first coating.
14. The method according to Claim 13, characterized in that said antimicrobial agent is a chlorhexidine salt, preferably chlorhexidine acetate, at a level in the range of 0.5 to 3% and silver sulfadiazine in an amount within the range of 0.5 to 5%.
15. The method according to Claim 13 or 14, characterized in that the first coating vehicle further comprises a biodegradable polymer.
16. An infection-resistant coating composition comprising a coating vehicle comprising a biomedical polyurethane in at least one solvent therefor and an antimicrobial agent comprising a silver salt and a biguanide.
17. A composition according to Claim 16, characterized in that the antimicrobial agent comprises a combination of silver sulfadiazine and chlorhexidine acetate.
18. A method of impregnating expanded PTFE medical devices, particularly vascular grafts, which comprise preparing a coating vehicle comprising biomedical polyurethane and a biodegradable polymer, preferably poly(lactic acid), in a solvent therefor, together with at least one member of a group consisting of chlorhexidine and its salts, and piperacil as antimicrobial agents, placing said graft in contact with the coating vehicle while under reduced atmospheric pressure, and drying the treated graft.
19. The process of Claim 18, characterized in that the coating vehicle contains 0.25 to 1% biomedical polyurethane, 0.25 to 1% poly(lactic acid), 1% chlorhexidine acetate and 3% piperacil in a solvent comprising 25% N-ethyl-2-pyrrolidone and 75% tetrahydrofuran.
20. An expanded PTFE vascular graft, a substantial portion of the interstices of which contains a coating composition comprising, by weight, one part biomedical polyurethane, one part poly(lactic acid), one part chlorhexidine acetate, and three parts piperacil.
21. A method of preparing an infection-resistant medical device which comprises:
 - (a) preparing a mixture of silver or a silver salt such as silver sulfadiazine or silver carbonate and a biguanide; and
 - (b) applying said mixture to the surface of a medical device.
22. The method of Claim 21, wherein the mixture is affixed to the surface of the device.
23. The method of Claim 21, wherein the mixture is applied to the surface as a powder.
24. The method of Claim 21, wherein the mixture is applied as an ingredient of a polymeric coating.

25. A method of preparing an infection-resistant medical device which comprises:
 (a) preparing a mixture of
 (i) a substance selected from the group consisting of chlorhexidine and its salts; and
 (ii) a silver salt selected from the group consisting of silver sulfadiazine, silver acetate, silver benzoate, silver iodate, silver laurate, silver protein, silver chloride, silver palmitate, silver oxide, silver carbonate and silver nitrate; and
 (b) applying the mixture to the surface of a medical device.
26. A method of preparing an infection-resistant medical device which comprises;
 (a) preparing a mixture of chlorhexidine acetate and silver sulfadiazine, in proportions by weight ranging from 1:9 to 9:1; and
 (b) applying the mixture to the surface of a medical device.
27. The method of Claim 26, characterized in that the mixture is present in a coating on the surface at a level in the range of 10 to 70% by weight.
28. A method according to Claim 21, which comprises:
 (a) preparing a powdered mixture of
 (i) a member of the group consisting of chlorhexidine and its salts; and
 (ii) a silver salt selected from the group consisting of silver sulfadiazine, silver oxide, silver carbonate and silver nitrate, silver acetate, silver benzoate, silver iodate, silver laurate, silver protein, silver chloride, silver palmitate;
 (b) treating a surface of a medical device to render it at least slightly adhesive; and
 (c) applying said powdered mixture to the surface of the medical device in a manner to cause adhesion of the powder thereto.
29. A method according to Claim 28, characterized in that the medical device is a glove, such as a latex glove.
30. The method of Claim 29, where the glove is a thermoplastic latex and characterized in that the powder is applied to the glove at a point in the manufacturing process where the glove surface is soft, whereby the powder particles adhere to the glove surface.
31. A method according to Claims 28, 29 or 30, characterized in that the mixture is applied by spraying a dry powdered mixture of dusting powder, a silver salt, and a biguanide.
32. A method according to Claim 28 or 29, characterized in that the mixture is applied by dipping the device into an aqueous or alcoholic slurry of dusting powder, a silver salt, and a biguanide.
33. A method of imparting infection-resistance to medical devices comprised of expanded PTFE materials comprising the step of applying to the device a coating vehicle comprising a biodegradable polymer, a silver salt and a biguanide.
34. A method of coating medical devices comprised of expanded PTFE materials to impart infection-resistance thereto comprising the steps of first dipping the device into a suspension of silver sulfadiazine, chlorhexidine acetate and biodegradable polymer in alcohol:tetrahydrofuran (10:90), followed by a second step of dipping the device into alcoholic silver nitrate solution.
35. The method of Claims 1, 3, 4 or 13 to 15, characterized in that the coating vehicle comprises a room temperature-curing biomedical silicone.
36. The method of Claim 1, 3, 4 or 13 to 15, characterized in that the coating vehicle comprises a mixture of a polydimethyl siloxane medical adhesive and a silicone fluid comprising an amino functional polydimethyl siloxane copolymer and mixed aliphatic and isopropanol solvents.

Patentansprüche

1. Verfahren zur Vorbereitung einer infektionsresistenten Oberfläche, dadurch gekennzeichnet, daß eine Beschichtungssträgersubstanz vorbereitet wird, indem ein matrixbildendes polymeres Material, das aus der

- aus biomedizinischen Polyurethan, biomedizinischen Silikonen und biologisch abbaubaren Polymeren und deren Kombinationen bestehenden Gruppe gewählt wird, in mindestens einem Lösemittel für diese vorbereitet wird, ein ein Silbersalz und ein Biguanid enthaltendes antimikrobielles Mittel in die Beschichtungsträgersubstanz eingemischt wird, um eine Beschichtungszusammensetzung zu bilden, die Oberfläche mit der Beschichtungszusammensetzung beschichtet wird, und die Beschichtung getrocknet wird.
2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das matrixbildende polymere Material biomedizinisches Polyurethan darstellt, vorzugsweise bei einer Konzentration im Bereich zwischen 1 und 10%.
 3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das matrixbildende polymere Material eine Mischung aus biomedizinischem Silikon und einem biologisch abbaubaren Polymer, vorzugsweise Poly(milchsäure) bei einer Konzentration im Bereich zwischen 0,2 und 2%, darstellt.
 4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das matrixbildende polymere Material eine Mischung aus biomedizinischem Silikon und biomedizinischem Polyurethan darstellt.
 5. Verfahren nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Lösemittel aus der aus Essigsäure, Methylacetat, Dimethylacetamid, Äthyl-2-pyrrolidon, N-(2-Hydroxyäthyl)-2-pyrrolidon, N-Cyclohexyl-2-pyrrolidon und deren Kombinationen bestehenden Gruppe gewählt wird.
 6. Verfahren nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß das besagte Silbersalz aus der aus Silberacetat, Silberbenzoat, Silbercarbonat, Silberjodat, Silberjodid, Silberlactat, Silberlaurat, Silbernitrat, Silberoxid, Silberpalmitat, Silberprotein und Silbersulfadiazin bestehenden Gruppe gewählt wird.
 7. Verfahren nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß das Biguanid ein Chlorhexidinsalz ist und vorzugsweise aus der aus Chlorhexidinacetat, Chlorhexidinglukonat, Chlorhexidihydrochlorid und Chlorhexidinsulfat bestehenden Gruppe gewählt ist.
 8. Verfahren nach einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß das antimikrobielle Mittel eine Kombination aus Silbersulfadiazin und einem Chlorhexidinsalz, vorzugsweise Chlorhexidinacetat, darstellt.
 9. Verfahren nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß die Oberfläche eine Oberfläche von einer medizinischen Vorrichtung, wie z.B. einem Katheter, einem Kontrazeptivum, einem Kondom, einem medizinischem Handschuh, einem Wundverband, einer Wundklammer, einem orthopädischen Implantat, einem Nahtmaterial, einem Arterientransplantat oder einem Leistenbruchpflaster darstellt.
 10. Verfahren nach einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, daß die besagte Oberfläche dazu beabsichtigt ist, mit unter Pflege stehenden Patienten in Kontakt zu kommen, wie z.B. die Oberfläche von einer Bettschüssel, einer Tischfläche, einem Krankenbett, die Oberfläche von einem chirurgischen Apparat oder eine Oberfläche in einem Operationssaal.
 11. Verfahren nach einem der vorstehenden Ansprüche, dadurch gekennzeichnet, daß mindestens ein antimikrobielles Mittel in der Beschichtungsträgersubstanz gelöst oder suspendiert ist.
 12. Verfahren nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß mindestens ein antimikrobielles Mittel in einem mit dem Lösemittel für das matrixbildende polymere Material mischbaren Lösemittel gelöst und nachträglich in die Beschichtungsträgersubstanz eingemischt wird.
 13. Verfahren zur Vorbereitung einer infektionsresistenten Oberfläche, dadurch gekennzeichnet, daß eine erste Beschichtungsträgersubstanz vorbereitet wird, indem ein biomedizinisches Polyurethan in ein dafür geeignetes Lösemittel, sowie wahlweise von 0,2 bis 2% Polymilchsäure dispergiert wird, und ein Silbersalz und ein Biguanid enthaltendes antimikrobielles Mittel darin eingemischt wird; daß eine zweite Beschichtungsträgersubstanz vorbereitet wird, indem ein biomedizinisches Silikon in einem dafür geeigneten Lösemittel dispergiert wird, vorzugsweise bei einer Konzentration von 0,5 bis 5%; daß die besagte erste Beschichtungsträgersubstanz auf die Oberfläche aufgetragen wird und darauf eine anhaftende erste Beschichtung bildet; und daß die besagte zweite Beschichtung über die besagte erste Beschichtung aufgetragen wird, um eine zweite, an die besagte erste Beschichtung haftende Beschichtung zu bilden.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß das besagte antimikrobielle Mittel ein Chlorhexidinsalz, vorzugsweise Chlorhexidinacetat bei einem Gehalt im Bereich zwischen 0,5 und 3% und Silber sulfadiazin bei einem Gehalt im Bereich zwischen 0,5 und 5% darstellt.
15. Verfahren nach Anspruch 13 oder 14, dadurch gekennzeichnet, daß die erste Beschichtungsträgersubstanz ferner ein biologisch abbaubares Polymer enthält.
16. Infektionsresistente Beschichtungszusammensetzung, die eine ein biomedizinisches Polyurethan in mindestens einem dafür geeigneten Lösemittel enthaltende Beschichtungsträgersubstanz sowie ein Silber Salz und ein Biguanid enthaltendes antimikrobielles Mittel enthält.
17. Zusammensetzung nach Anspruch 16, dadurch gekennzeichnet, daß das antimikrobielle Mittel aus einer Kombination von Silbersulfadiazin und Chlorhexidinacetat besteht.
18. Verfahren zur Imprägnierung von medizinischen Vorrichtungen aus Schaum-PTFE, besonders Gefäßtransplantaten, das beinhaltet, daß eine Beschichtungsträgersubstanz, die biomedizinisches Polyurethan und ein biologisch abbaubares Polymer, vorzugsweise Poly(milchsäure), in einem dafür geeigneten Lösemittel enthält, zusammen mit mindestens einem Mitglied einer aus Chlorhexidin und dessen Salze bestehenden Gruppe und Piperacillin als antimikrobielle Mittel, vorbereitet, das besagte Transplantat unter reduziertem atmosphärischen Druck mit der Beschichtungsträgersubstanz in Kontakt gebracht und das behandelte Transplantat getrocknet wird.
19. Verfahren nach Anspruch 18, dadurch gekennzeichnet, daß die Beschichtungsträgersubstanz 0,25 bis 1% biomedizinisches Polyurethan, 0,25 bis 1% Poly(milchsäure), 1% Chlorhexidinacetat und 3% Piperacillin in einem aus 25% N-Äthyl-2-pyrrolidon und 75% Tetrahydrofuran bestehenden Lösemittel enthält.
20. Gefäßtransplantat aus Schaum-PTFE, bei dem ein bedeutender Anteil der Zwischenräume eine Beschichtungszusammensetzung enthält, die einen Gewichtsteil biomedizinisches Polyurethan, einen Gewichtsteil Poly(milchsäure), einen Gewichtsteil Chlorhexidinacetat und drei Gewichtsteile Piperacillin enthält.
21. Verfahren zur Vorbereitung einer infektionsresistenten medizinischen Vorrichtung, das beinhaltet, daß
 - (a) eine Mischung aus Silber oder einem Silbersalz wie z.B. Silbersulfadiazin oder Silbercarbonat und einem Biguanid vorbereitet wird; und
 - (b) die besagte Mischung auf die Oberfläche einer medizinischen Vorrichtung aufgetragen wird.
22. Verfahren nach Anspruch 21, wobei die Mischung an der Oberfläche der Vorrichtung befestigt wird.
23. Verfahren nach Anspruch 21, wobei die Mischung als Pulver auf die Oberfläche aufgetragen wird.
24. Verfahren nach Anspruch 21, wobei die Mischung als Bestandteil einer polymeren Beschichtung aufgetragen wird.
25. Verfahren zur Vorbereitung einer infektionsresistenten medizinischen Vorrichtung, das beinhaltet, daß
 - (a) eine Mischung aus
 - (i) einer aus der aus Chlorhexidin und dessen Salze bestehenden Gruppe gewählten Substanz; und
 - (ii) einem aus der aus Silbersulfadiazin, Silberacetat, Silberbenzoat, Silberjodat, Silberlaurat, Silberprotein, Silberchlorid, Silberpalmitat, Silberoxid, Silbercarbonat und Silbernitrat bestehenden Gruppe gewählten Silbersalz vorbereitet wird; und
 - (b) die Mischung auf die Oberfläche einer medizinischen Vorrichtung aufgetragen wird.
26. Verfahren zur Vorbereitung einer infektionsresistenten medizinischen Vorrichtung, das beinhaltet, daß
 - (a) eine Mischung aus Chlorhexidinacetat und Silbersulfadiazin in einem Gewichtsverhältnis zwischen 1:9 und 9:1 vorbereitet wird; und
 - (b) die Mischung auf die Oberfläche einer medizinischen Vorrichtung aufgetragen wird.
27. Verfahren nach Anspruch 26, dadurch gekennzeichnet, daß die Mischung bei einem Gehalt von 10 bis 70 Gew.-% in einer Beschichtung auf der Oberfläche vorhanden ist.
28. Verfahren nach Anspruch 21, das beinhaltet, daß

- (a) eine pulverförmige Mischung aus
- (i) einem Mitglied der aus Chlorhexidin und dessen Salze bestehenden Gruppe; und
 - (ii) einem aus der aus Silbersulfadiazin, Silberoxid, Silbercarbonat und Silbernitrat, Silberacetat, Silberbenzoat, Silberjodat, Silberlaurat, Silberprotein, Silberchlorid, Silberpalmitat bestehenden Gruppe gewählten Silbersalz vorbereitet wird;
- (b) die Oberfläche einer medizinischen Vorrichtung so behandelt wird, daß sie mindestens etwas haftend wird; und
- (c) die besagte pulverförmige Mischung auf die Oberfläche der medizinischen Vorrichtung aufgetragen wird, auf eine solche Weise, daß Haftung des Pulvers an der Oberfläche stattfindet.
29. Verfahren nach Anspruch 28, dadurch gekennzeichnet, daß die medizinische Vorrichtung ein Handschuh ist, wie z.B. ein Latexhandschuh.
30. Verfahren nach Anspruch 29, wobei der Handschuh ein thermoplastisches Latex darstellt und dadurch gekennzeichnet, daß das Pulver auf den Handschuh zu einer Zeit im Herstellungsprozess aufgetragen wird, zu der die Handschuhoberfläche weich ist, wodurch die Pulverteilchen an der Handschuhoberfläche haften.
31. Verfahren nach den Ansprüchen 28, 29 oder 30, dadurch gekennzeichnet, daß die Mischung durch Sprühen einer trockenen, pulverförmigen Mischung aus Körperpuder, einem Silbersalz und einem Biguanid aufgetragen wird.
32. Verfahren nach Anspruch 28 oder 29, dadurch gekennzeichnet, daß die Mischung dadurch aufgetragen wird, daß die Vorrichtung in eine wässrige oder alkoholische Aufschlämmung aus Körperpuder, einem Silbersalz und einem Biguanid getaucht wird.
33. Verfahren zur Verleihung von Infektionsresistenz an Schaum-PTFE -Materialien bestehende medizinische Vorrichtungen, das den Schritt beinhaltet, daß eine ein biologisch abbaubares Polymer, ein Silbersalz und ein Biguanid enthaltende Beschichtungsträgersubstanz auf die Vorrichtung aufgetragen wird.
34. Verfahren zur Beschichtung von aus Schaum-PTFE-Materialien bestehenden medizinischen Vorrichtungen, um diesen Infektionsresistenz zu verleihen, das die Schritte beinhaltet, daß die Vorrichtung zunächst in eine Suspension aus Silbersulfadiazid, Chlorhexidinacetat und biologisch abbaubarem Polymer in Alkohol-Tetrahydrofuran (10:90) getaucht wird, und die Vorrichtung dann in einem zweiten Schritt in alkoholische Silbernitratlösung getaucht wird.
35. Verfahren der Ansprüche 1, 3, 4 oder 13 bis 15, dadurch gekennzeichnet, daß die Beschichtungsträgersubstanz ein bei Raumtemperatur aushärtendes biomedizinisches Silikon enthält.
36. Verfahren der Ansprüche 1, 3, 4 oder 13 bis 15, dadurch gekennzeichnet, daß die Beschichtungsträgersubstanz eine Mischung aus einem medizinischen Polydimethylsiloxan-Klebstoff und einer ein aminofunktionalisiertes Polydimethylsiloxan-Copolymer und gemischte aliphatische und Isopropanolösmittel enthaltenden Silikonflüssigkeit enthält.

Revendications

1. Méthode de préparation d'une surface résistante aux infections, caractérisée par la préparation d'un véhicule de revêtement par dispersion d'une matière polymère à formation de matrices sélectionnée dans le groupe comprenant polyuréthane biomédical, silicones biomédicaux, polymères biodégradables et combinaisons de ceux-ci, dans au moins un solvant approprié, incorporant un agent antimicrobien comprenant sel d'argent et biguanide dans le véhicule de revêtement pour former une composition de revêtement, l'application de la composition de revêtement sur la surface, et le séchage du revêtement.
2. Méthode de la revendication 1, caractérisée en ce que la matière polymère à formation de matrices est un polyuréthane biomédical de préférence à une concentration variant entre 1 et 10 %.
3. Méthode de la revendication 1, caractérisée en ce que la matière polymère à formation de matrices est un mélange de silicone biomédicale et de polymère biodégradable, de préférence l'acide polylactique, à

une concentration variant entre 0,2 et 2 %.

4. Méthode de la revendication 1, caractérisée en ce que la matière polymère à formation de matrices est un mélange de silicone biomédicale et de polyuréthane biomédical.
5. Méthode de l'une quelconque des revendications 1 à 4, caractérisée en ce que le solvant est sélectionné dans le groupe comprenant acide acétique, acétate de méthyle, diméthylacétamide, pyrrolidone-2 d'éthyle, N-(2-hydroxyéthyl)-2-pyrrolidone, N-cyclohexyl-2-pyrrolidone, et combinaisons de ceux-ci.
- 10 6. Méthode suivant l'une quelconque des revendications qui précèdent, caractérisée en ce que ledit sel d'argent est sélectionné dans le groupe comprenant acétate d'argent, benzoate d'argent, carbonate d'argent, iodate d'argent, iodure d'argent, lactate d'argent, laurate d'argent, nitrate d'argent, oxyde d'argent, palmitate d'argent, protéine d'argent et sulfadiazine d'argent.
- 15 7. Méthode suivant l'une quelconque des revendications qui précèdent, caractérisée en ce que le biguanide est un sel de chlorhexidine et est de préférence sélectionné dans le groupe comprenant acétate de chlorhexidine, gluconate de chlorhexidine, hydrochlorure de chlorhexidine et sulfate de chlorhexidine.
- 20 8. Méthode suivant l'une quelconque des revendications 1 à 5, caractérisée en ce que l'agent antimicrobien est une combinaison de sulfadiazine d'argent et d'un sel de chlorhexidine, de préférence l'acétate de chlorhexidine.
- 25 9. Méthode suivant l'une quelconque des revendications qui précèdent, caractérisée en ce que la surface est une surface d'un dispositif médical tel qu'un cathéter, un contraceptif, un préservatif, un gant médical, un pansement de plaie, une pince de plaie, un implant orthopédique, une suture, un greffon artériel ou une pièce de réparation d'hernie.
- 30 10. Méthode suivant l'une quelconque des revendications 1 à 8, caractérisée en ce que ladite surface en est une destinée à venir en contact avec les patients, telle qu'une surface de bassin, un dessus de table, un lit de patient, la surface d'un appareil chirurgical ou la surface d'une salle d'opération.
- 35 11. Méthode de l'une quelconque des revendications qui précèdent, caractérisée en ce qu'au moins un agent antimicrobien est dissous ou en suspension dans le véhicule de revêtement.
- 40 12. Méthode de l'une quelconque des revendications 1 à 10, caractérisée en ce qu'au moins un agent antimicrobien est dissous dans un solvant miscible avec le solvant pour la matière polymère à formation de matrices et qui est subséquentement incorporé dans le véhicule de revêtement.
- 45 13. Méthode de préparation d'une surface résistant aux infections, caractérisée par la préparation d'un premier véhicule de revêtement par dispersion d'un polyuréthane biomédical dans un solvant approprié, et au choix de 0,2 à 2 % d'acide polylactique, et l'incorporation d'un agent antimicrobien comprenant sel d'argent et biguanide ; la préparation d'un deuxième véhicule de revêtement par dispersion d'une silicone biomédicale dans un solvant approprié, de préférence à une concentration variant entre 0,5 et 5 % ; l'application du premier véhicule de revêtement sur la surface en le laissant former une première couche adhésive ; et l'application du deuxième revêtement sur le premier de manière à former une deuxième couche adhérent à la première.
- 50 14. Méthode suivant la revendication 13, caractérisée en ce que ledit agent antimicrobien est un sel de chlorhexidine, de préférence l'acétate de chlorhexidine, à un taux variant entre 0,5 et 3 %, et la sulfadiazine d'argent à un taux variant entre 0,5 et 5 %.
- 55 15. Méthode suivant la revendication 13 ou 14, caractérisée en ce que le premier véhicule de revêtement comprend également un polymère biodégradable.
16. Composition de revêtement résistant aux infections, comprenant un véhicule de revêtement comprenant un polyuréthane biomédical dans au moins un solvant approprié et un agent antimicrobien comprenant sel d'argent et biguanide.
17. Composition suivant la revendication 16, caractérisée en ce que l'agent antimicrobien comprend une combinaison de sulfadiazine d'argent et d'acétate de chlorhexidine.

18. Méthode d'imprégnation des dispositifs médicaux en PTFE expansé, particulièrement les greffons vasculaires, qui comprend la préparation d'un véhicule de revêtement comprenant un polyuréthane biomédical et un polymère biodégradable, de préférence l'acide polylactique, dans un solvant approprié, ainsi qu'au moins un membre d'un groupe comprenant la chlorhexidine et ses sels, et la pipéracilline comme agents antimicrobiens, la mise dudit greffon en contact avec le véhicule de revêtement sous pression atmosphérique réduite, et le séchage du greffon traité.
19. Le processus de la revendication 18, caractérisé en ce que le véhicule de revêtement contient de 0,25 à 1 % de polyuréthane biomédical, de 0,25 à 1 % d'acide polylactique, 1 % d'acétate de chlorhexidine, et 3 % de pipéracilline dans un solvant comprenant 25 % de N-éthyl-2-pyrrolidone et 75 % de tétrahydrofuranne.
20. Un greffon vasculaire en PTFE expansé, dont une partie importante des interstices contient une composition de revêtement comprenant, par poids, une partie de polyuréthane biomédical, une partie d'acide polylactique, une partie d'acétate de chlorhexidine, et trois parties de pipéracilline.
21. Méthode de préparation d'un dispositif médical résistant aux infections qui comprend :
- (a) la préparation d'un mélange d'argent ou de sel d'argent tel que la sulfadiazine d'argent ou le carbonate d'argent et d'un biguanide ; et
 - (b) l'application dudit mélange sur la surface d'un dispositif médical.
22. Méthode de la revendication 21, suivant laquelle le mélange est apposé sur la surface du dispositif.
23. Méthode de la revendication 21, suivant laquelle le mélange est appliqué en poudre sur la surface.
24. Méthode de la revendication 21, suivant laquelle le mélange est appliqué en tant qu'ingrédient d'un revêtement polymère.
25. Méthode de préparation d'un dispositif médical résistant aux infections qui comprend :
- (a) la préparation d'un mélange
 - (i) d'une substance sélectionnée dans le groupe comprenant la chlorhexidine et ses sels ; et
 - (ii) d'un sel d'argent sélectionné dans le groupe comprenant sulfadiazine d'argent, acétate d'argent, benzoate d'argent, iodate d'argent, laurate d'argent, protéine d'argent, chlorure d'argent, palmitate d'argent, oxyde d'argent, carbonate d'argent et nitrate d'argent ; et
 - (b) l'application du mélange sur la surface d'un dispositif médical.
26. Méthode de préparation d'un dispositif médical résistant aux infections qui comprend :
- (a) la préparation d'un mélange d'acétate de chlorhexidine et de sulfadiazine d'argent, en proportions, par poids, variant entre 1:9 et 9:1 ; et
 - (b) l'application du mélange sur la surface d'un dispositif médical.
27. Méthode de la revendication 26, caractérisée en ce que le mélange est présent dans un revêtement sur la surface à un taux variant entre 10 et 70 % par poids.
28. Méthode suivant la revendication 21, qui comprend :
- (a) la préparation d'un mélange en poudre
 - (i) d'un membre du groupe comprenant la chlorhexidine et ses sels ; et
 - (ii) d'un sel d'argent sélectionné dans le groupe comprenant sulfadiazine d'argent, oxyde d'argent, carbonate d'argent et nitrate d'argent, acétate d'argent, benzoate d'argent, iodate d'argent, laurate d'argent, protéine d'argent, chlorure d'argent et palmitate d'argent ;
 - (b) le traitement de la surface d'un dispositif médical pour le rendre au moins légèrement adhésif ; et
 - (c) l'application dudit mélange en poudre sur la surface du dispositif médical de manière à faire adhérer la poudre au dispositif.
29. Méthode suivant la revendication 28, caractérisée en ce que le dispositif médical est un gant, tel qu'un gant en latex.
30. Méthode de la revendication 29, où le gant est un latex thermoplastique et caractérisée en ce que la poudre est appliquée sur le gant à un stade du processus de fabrication où la surface du gant est molle, ce qui permet aux particules de poudre d'adhérer à la surface du gant.

31. Méthode suivant les revendications 28, 29 ou 30, caractérisée en ce que le mélange est appliqué par vaporisation d'un mélange poudreux sec de poudre à saupoudrer, de sel d'argent et de biguanide.
- 5 32. Méthode suivant la revendication 28 ou 29, caractérisée en ce que le mélange est appliqué par immersion du dispositif dans une boue aqueuse ou alcoolique de poudre à saupoudrer, de sel d'argent et de biguanide.
- 10 33. Méthode d'attribution de résistance aux infections aux dispositifs médicaux faits de PTFE expansé comprenant l'étape d'application sur le dispositif d'un véhicule de revêtement comprenant polymère biodégradable, sel d'argent et biguanide.
- 15 34. Méthode de revêtement des dispositifs médicaux faits de PTFE expansé de manière à les rendre résistants aux infections, comprenant les étapes d'immersion préalable du dispositif dans une suspension de sulfadiazine d'argent, d'acétate de chlorhexidine et de polymère biodégradable dans un mélange alcool-tétrahydrofuranne (10:90), suivie d'une deuxième étape d'immersion du dispositif dans une solution alcoolique de nitrate d'argent.
- 20 35. Méthode des revendications 1, 3, 4 ou 13 à 15, caractérisée en ce que le véhicule de revêtement comprend une silicone biomédicale durcissant à température ambiante.
- 25 36. Méthode des revendications 1, 3, 4 ou 13 à 15, caractérisée en ce que le véhicule de revêtement comprend un mélange d'adhésif médical à base de siloxane polydiméthylrique et d'une silicone liquide comprenant un copolymère de siloxane polydiméthylrique fonctionnalisé par addition de groupes aminés ainsi que des solvants mixtes aliphatiques et d'isopropanol.